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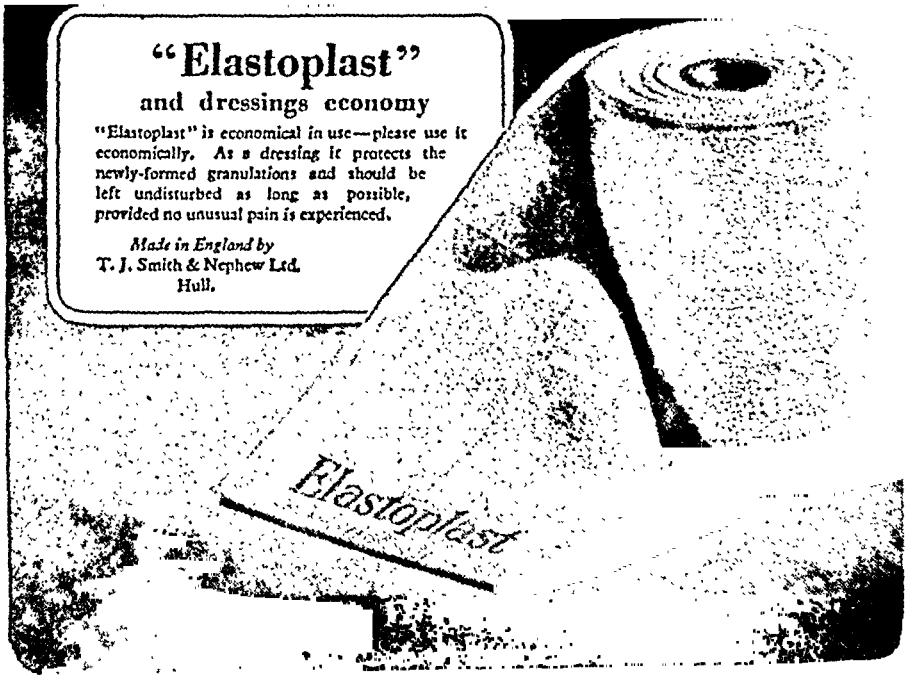

Edinburgh Medical Journal

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PROPHYLAXIS FROM THE OBSTETRICAL AND GYNÆCOLOGICAL STANDPOINT *

By R. W. JOHNSTONE, *C.B.E.*, M.D., F.R.C.S.Ed., F.R.C.O.G.

No branch of modern medicine is more imbued with the spirit of prevention than obstetrics. This is no idle boast; it is the natural outcome of the growth of preventive medicine, because reproduction, while not an essential of individual life or health, is the prime essential of the continuance of the race, and the welfare of the mother and child must therefore be recognised as a vital matter in all enlightened civilisations. Obstetrics and pediatrics are therefore found to make more contacts than medicine and surgery with the activities of public health work as we have known it, and this close relationship must continue in the wider social medicine of to-morrow.

Despite the claim which I have just made, it still remains true that fully one-half of all the gynæcological beds in our hospitals are occupied by women suffering from the immediate or remote results of childbirth, and since "good obstetrics is preventive gynæcology" it becomes obvious that our obstetrics is not yet good enough.

Good obstetrics in these days of ours presents three aspects. The most important must always be the care of the mother and child during delivery—intra-natal care. But the advent and development in our own day of ante-natal care, and more recently of its natural complement, organised post-natal care, have greatly increased the preventive field of the modern obstetrician.

Ante-natal Care

It is unfortunately true that all the high hopes which were inspired by the new gospel of ante-natal care in the early years of this century have not yet been fulfilled. Nevertheless much has been accomplished both directly and indirectly. Directly by the diminished incidence of, and diminished mortality from, some of the more serious diseased conditions arising out of pregnancy; indirectly by the greatly increased public interest in maternity in the last twenty-five years and in the

* Given under the Thom Bequest for the advancement of prevention of chronic disease with special reference to Cancer, 21st November 1944.

gradual raising of the standard of midwifery practice, both of which, I think, may in considerable degree be traced to the stimulus of the new outlook.

It would be tedious even if it were possible to prove these claims by statistics. The best proof of the value of ante-natal care is that there is no obstetrician who would willingly revert to the days when there was none, and that the call at present is all for more ante-natal beds in our maternity hospitals.

One of the diseases which we hoped to see rapidly diminish as a result of the introduction of ante-natal care was *eclampsia* with its usual precursor, pre-eclamptic toxæmia. Together these have long been one of the major causes of maternal mortality and morbidity. Since we have every reason to regard them as peculiar to pregnancy and since the early stages of pre-eclamptic toxæmia are not irresponsive to treatment, it was natural to hope that we should soon gain the mastery over it. That hope has not been realised, but something has been gained. In Scotland in the ten years 1921-30 the average death-rate from eclampsia per 100,000 live births was 108; in the next decade —1931-40—it was 80·4; or, to put it in another way, there were only 764 deaths from eclampsia in the latter decade as against 1366 in the earlier corresponding period. Part of the explanation for this comparative failure may possibly be found in the view that this toxæmia occurs in women constitutionally predestined to arterial hypertensive disease. If that should be proved to be true then, of course, our expectations in regard to its prevention must be drastically limited.

The bearing of these figures on the prevention of chronic disease lies in the fact that apart from those women who die from eclampsia or severe pre-eclamptic toxæmia, some 50 per cent. of those who recover are left with some permanent damage to the arterio-renal system which shows itself later in the recurrence of toxæmic pregnancy, in accidental hæmorrhage and repeated abortions, in chronic nephritis or in chronic hypertension. One of the positive findings which has emerged from the ante-natal study of pre-eclamptic toxæmia is that the longer the condition is allowed to continue, the greater appears to be the tendency to subsequent hypertension and the greater the liability to recurrence of toxæmia in subsequent pregnancies. I assume that the gradual drop in the mortality rate from eclampsia reflects a diminished incidence of the more serious forms of pre-eclamptic toxæmia, and that this in its turn is to be credited to the increasing exercise of *routine* ante-natal care. For the benefit of those who are not familiar with the subject, I would underline the word "routine," for the early stages of this disease, in which it is most amenable to treatment, are frequently devoid of any subjective symptoms, and are recognised only by the routine examination of the arterial pressure, the urine and the body-weight at regular intervals.

Although the figures in connection with *hyperemesis gravidarum*

do not generally show any dramatic improvement, yet I think that a great deal could be done in regard to it if my interpretation of the experience in our hospital is correct. In 1923, the first year for which we have complete records at the Royal Maternity Hospital, no fewer than 16 per cent. of the patients sent in with this condition succumbed. Since then the number of such cases sent in has increased very considerably, and the patients have been sent in much *earlier* in the course of the disease. As the numbers have gone up, the deaths have gone down until in 1939 the mortality was nil, and in the four years since there has been only one death in over 150 cases. My interpretation of this is that it is the result of the teaching of ante-natal care.

Other examples of the preventive value of ante-natal care are to be seen in the treatment of urinary infections, so prone to occur in pregnancy, and in the results of the closer supervision of the diet of the expectant mother. I might refer you, for example, to the latest reports by Professor Stanley Davidson and Dr Fullerton on the subject of anæmia amongst pregnant women, which show that in Edinburgh and Aberdeen there has been a gratifying improvement in recent years, or to a report on the Incidence of Rickets in Wartime by the British Pediatric Association which proves that rickets as revealed by radiological examination has been enormously reduced in frequency. Again there are several reports available of large-scale experimental observations on the nutrition of pregnant women which indicate the benefits of a scientifically arranged diet. In particular, such experiments seem to have been successful in reducing the incidence of abortion and premature births, and it is these latter that do so much to swell the infant mortality rate.

Intra-Natal Care

Here the question of chronic disease in relation to obstetrics centres largely round "Maternal Disablement." The disablement is largely due to the effects of puerperal infection, but includes also the effects of hæmorrhage, toxæmia, nervous and mental shock and the increased damage done to already diseased organs such as the heart.

Sir Halliday Croom used to teach that no woman ever completely recovered from an acute puerperal infection. In those days recovery was the outcome of a battle between the infecting organisms and the patient's powers of resistance, and was but little affected by drugs or any form of specific therapy. Perhaps there was an element of picturesque exaggeration in Croom's rather characteristic sweeping statement, but there was also as much truth as is generally found in an epigram. For the processes by which nature overcomes an acute infection centred in the lower abdomen and pelvis are liable to leave the battlefield in a state of disorder from which complete recovery is rare—adhesions causing or perpetuating displacements of the

uterus, tubes and ovaries, and interfering with proper function, sclerosis of tissues, and it may be residual foci of infection. Hence a melancholy toll of symptoms—the discomfort of leucorrhœa, the debilitating influence of menstrual disorders, the sapping of courage by constant pelvic pain, the depressing frustration of sterility, and the fell spectre of dyspareunia which wrecks the happiness of more marriages than anyone but the gynæcologist and the medical psychologist can guess at—all leading directly or indirectly to neurasthenia and psychasthenia with their incalculable potentialities of bodily disablement, mental ill-health and unhappiness.

Two closely related questions present themselves in this connection in these days of ours when we have more effective methods of combating infection: (1) How many women are disabled in some degree by the conditions to which I have referred? and (2) have our newer methods diminished the incidence of these sequelæ?

In his Ingleby Lectures at Birmingham in 1931 the late Professor Blair Bell discussed the first subject, and estimated that for every woman who died as a direct result of childbirth, at least twenty were more or less permanently disabled. No obstetrician challenged at that time the accuracy of this estimate of the ratio of the killed and wounded, but the changes that have taken place since 1931 consequent upon the discovery of streptocidal drugs of the sulphonamide group make it desirable to ask ourselves if the ratio still holds good. At that time close upon 3000 women died every year in childbirth or of its direct results in England and Wales. The corresponding figures for Scotland were 650. The numbers of women disabled were therefore on Blair Bell's estimate some 60,000 in England and Wales and 13,000 in Scotland.

By 1942 the total maternal death-rates had fallen to 1360 for England and Wales and 382 for Scotland. Assuming the ratio of 20 to 1, the disablement figures would be about 27,000 for England and Wales and 7600 for Scotland. Obviously, therefore, the gross amount of maternal disablement must be greatly less than in 1931, but questions remain as to where the credit for the improvement lies and as to whether the disablement ratio is still to be assumed to be as before.

Mr Kyd, the Registrar-General for Scotland, has kindly supplied me with figures which elucidate the first point. "Maternal deaths" may be broadly divided into those due to "sepsis" and those due to all "other causes." If we compare two five-year periods—the first from 1931 to 1935 and the second from 1936 to 1940—we find that there was an improvement in the death-rate from sepsis equivalent to 33 per cent. in England and Wales and to 42 per cent. in Scotland; while the death-rates from "other causes" had diminished only by 12 per cent. in England and Wales and 10 per cent. in Scotland. This means that the total improvement is very largely due to the fall in the death-rate from sepsis. The actual figures show that the striking diminution

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in the deaths from sepsis began in 1937, and this corresponds with the wide employment of the sulphonamide group of drugs.

With regard to the second question—whether the ratio of 20 women disabled to every one that dies is still applicable—I find it impossible to give a definite opinion, but I think we may reasonably assume that the incidence of the more serious sequelæ of pelvic infection has been diminished by sulphonamide therapy in a proportion not greatly less than that of the actual death-rate. My strong *impression*, for what it is worth, is that we see, for example, many fewer cases of pyosalpinx resulting from *puerperal* infection than we used to do ten or fifteen years ago.

But the prevention of puerperal sepsis is far from being the only way in which intra-natal care can exercise its preventive benefits. To discuss the others would take too much time and lead me far into the realm of pure obstetrics. Perhaps I can serve the present purpose better by saying that in this century we have been witnessing two important changes coming over obstetrics. One is that, as a result of the close association of obstetrics with gynæcology, obstetricians have become more and more surgically minded; the other that at the same time they have become more conservative, more content to allow a natural function to pursue its natural course. Our operative methods and results have improved enormously, and when this is considered along with the conservative teaching just mentioned one begins to realise the extent to which the old-fashioned meddlesome midwifery, the unnecessary and often blindly empirical use of the forceps, for example, is being eliminated, and with it a dire toll of minor and major injuries to the maternal passages.

Post-natal Care

This is a more recent corollary of ante-natal care. It implies the "follow-up" of the patient for two or three months after the end of the lying-in period, and the obstetrician's attention is devoted to noting the progress of all that is implied by the term "involution" in the birth canal, the healing of lacerations, the recovery of muscular and ligamentous tone, the promotion of natural lactation and the treatment of any disorders of the circulatory, renal, respiratory or other systems which may have been involved in special cases. Cervical infections are treated and cured; the correct position of the uterus is secured; postural strains of the pelvic and pelvi-lumbar joints are treated if necessary. In this way a great deal can be and is actually being done to prevent a multitude of minor complaints and much chronic partial invalidism.

While it is gratifying to recognise in the Maternity Services (Scotland) Act of 1937 that the Public Health Authorities in this country are alive to the needs of the situation, much still requires to

be done. In particular a coherently organised maternity service for the whole of the United Kingdom should be established as the best means of improving the practice of obstetrics. One of the main desiderata of any such service is that the same obstetricians, or at least the same obstetric team, should be responsible for the woman throughout the ante-, intra- and post-natal periods. The present isolation of much of our ante-natal work is probably one of the main reasons why its results have fallen short of our expectations. Such a service should ensure that every woman would get adequately skilled attention during pregnancy, in labour and after delivery, and it should provide additional facilities for the more complete rehabilitation of those women who need special post-puerperal care. I think that we can learn something of great value from our experience during the present war. Emergency maternity hospitals have been established in several large country-houses with spacious surroundings, but within reach of specialist obstetric supervision. After visiting such places my mind has been left with no doubts as to the beneficial preventive influence of the good surroundings and generous diet in these hospitals, and I hope that they may be continued after the war both for patients whose deliveries are likely to be normal and for purposes of rehabilitation. Apart from anything else, such rehabilitation and convalescent hostels for mothers would tend to encourage breast-feeding, for most of the mothers who give up breast-feeding within a week or two of leaving hospital, do so because they have become discouraged by some comparatively trivial difficulties with which they have neither the knowledge nor the perseverance to cope successfully. By this means we might hope to do much to diminish the infant mortality, which is such a blot on the records of Scotland.

Cancer

If it has been comparatively easy to survey the many and far-reaching preventive features of good obstetrics, it is quite the reverse in regard to the rôle of gynæcology in the prevention of cancer. The causes of disease in mothers and infants arising out of childbirth are comparatively well understood, and preventive measures can be devised. The causes of cancer on the other hand are still almost wholly unknown, and therefore we can only grope in the dark for preventive measures. Nevertheless it is necessary to consider how our knowledge of the causes of cancer is being sought out, since preventive hints may be gleaned even in advance of assured knowledge.

The problem of cancer is being attacked along three main lines. The first is the clinical observation of the disease in man, especially of its earliest stages, and of its reactions to treatment. In that attack most of us can take some share, however humble.

The second is the line of experimental research in regard to the production of cancer in animals. This is a highly specialised form

of work, and while its results can often be rightly assessed only by experts, yet we can all appreciate the more obvious ways in which experimental observations are yielding suggestive information, albeit by the slow scriptural method of "line upon line, here a little and there a little."

The third line of attack is by the collection and analysis of statistical observations. It seems to stand to reason that if we can collect and analyse data regarding the incidence of the disease in different races and in different regions of the world with their differences in customs and diet, in different organs of the body, in different social and economic groups, we ought to progress in a sort of converging spiral from the outside of the problem, gradually narrowing it down more and more until ultimately we reach a central point where logically there must be a causal factor.

Statistical study has enabled us to correct our earlier impression that cancer was a disease mainly restricted to man, and that it was on the increase as a result of our so-called civilisation. The investigations of Bashford and others showed that in animals, either domesticated or wild, which are enabled to live to what correspond to the older age periods of the life of man, cancer is a common disease. Geographical studies have revealed that cancer is prevalent among the less civilised races, although the observations are not sufficiently extensive or accurate to provide any reliable comparison of its relative frequency in the two main groups. "The idea that cancer is a disease of civilisation rests," as Gideon Wells has said, "on the most worthless of evidence." That it still appears in one form or another in medical literature is a deplorable illustration of the principle so aptly called by Wilfred Trotter "the mysterious viability of the false" (Cramer [1]).

These findings are important as they help to confirm the identity of experimental cancer in animals with cancer as it spontaneously occurs both in man and animals, and thus they establish the validity of applying our experimentally-gained knowledge of the one to the other. For example, cancer can be produced experimentally in young animals as easily as in older ones, and therefore we may conclude that it is not senility of the tissues which makes cancer so much more common in old people than in young, but rather that the carcinogenic factor acts so slowly that much of the span of life has passed before its results are recognisable. Incidentally this has a profound bearing upon the question of prevention, for in the case of man a period of ten to twenty years must be allowed to elapse before any conclusions as to the value or otherwise of any form of prevention can be legitimately drawn. Another conclusion which may be drawn from this need for prolonged action of the carcinogenic factor as well as from experimental evidence is that in all probability there are two factors at work—one, a slowly acting remote, possibly constitutional cause, and the other, a more immediate cause which makes the normal cell more or less suddenly adopt disorderly growth.

Studies of the geographical distribution of cancer of different organs have revealed curious variations, and analyses of these have shown significant variations in relation to such points as occupation, dietary habits and social status. Thus Dr Percy Stocks,[2] the Medical Statistical Officer to the Registrar-General for England and Wales, has investigated the local incidence of deaths from cancer of the uterus, breast and other organs. (In regard to the uterus he takes cancer of the corpus uteri and the cervix together, but cancer of the corpus forms so small a proportion of the total of uterine cancer that one may safely take his results as applicable to cancer of the cervix.) Amongst the curious results of this enquiry Stocks found that areas with the highest death-rate from cancer of the cervix under the age of 65 showed the lowest death-rate from breast cancer; and that while the death-rate from cervical cancer increases steadily as we go down the social scale from wives of professional men to those of unskilled labourers, the death-rate from breast cancer does precisely the opposite.

These observations are apparently rather conflicting, and in the search for any common factor one turns to the thought of the sex hormones, which originate in the ovary and influence the functions of both the uterus and the breast.

On the one side we have the well-known facts that the œstrogenic hormone of the ovary is essentially a growth-producing hormone, and there is clear experimental evidence that when administered in excess over a prolonged period to mice which are of a cancer-susceptible strain, and which have been nursed by their mothers so that they have received also the milk-borne carcinogenic factor discovered by the brilliant experiments of Bittner,[3] cancer of the breast is easily produced. Cancer of the cervix, a site which is also in some measure physiologically influenced by the œstrogenic hormone, has also been produced experimentally in this way; and even sarcoma has been produced at the site of injection in the inter-scapular region—a point of particular interest since the tissues in that region are not normally subject to œstrogenic reaction. All this demonstrates beyond dubiety that œstrogenic hormone plays some part in the growth of tumours in mice and other experimental animals, but no significant evidence has ever been produced to show that the administration of the same hormone can cause tumour growth in human beings.

On the other side, we have the facts that deprivation of the œstrogenic hormone is apparently followed by some retardation of growth in spontaneous breast cancer both in animals and in human beings. Some of us remember that many years ago Beatson of Glasgow advocated oöphorectomy in the treatment of mammary cancer, and more recently some improvement has been found to follow X-rays sterilisation of such patients before the menopausal age. There is, however, little evidence that the benefit is other than temporary.

Along the same lines efforts have been made to produce benefit in such cases by the administration of androgenic hormones, which in effect is a chemical castration of the woman, and some success has followed in cases of secondary metastases in bones.[4] The undoubted success, even if it be only temporary, of the administration of synthetic œstrogens in the prostatic cancer of the male is an interesting example of a similar chemical castration in the other sex, œstrogens having been proved experimentally to produce atrophy of the prostate and a diminished output of the androgenic steroids, possibly through their damping down the activity of the anterior pituitary lobe.

So far these observations seem to form a coherent picture, but a disturbing factor is introduced by yet other observations. There are on record a number of cases of improvement, again probably only temporary, in breast cancer under the administration of stilboestrol especially in women past the menopausal age. Haddow[5] and his collaborators have had some similar results with other synthetic œstrogens in cancer of other organs as well as the breast, and have also produced experimental evidence[6] of the paradox that œstrogens, which as I have said are essentially growth-producing, can in certain circumstances cause at least a temporary inhibition of growth.

When we consider all these points and ask ourselves whether any firm deductions are to be drawn from them, the answer would appear to be that whilst no causal relationship can be clearly seen at present between the development of cancer in human beings and the endocrine secretions, yet they obviously do have some influence on the acceleration and retardation of growth in some forms of cancer. The mind lingers with the speculation as to whether it may be the unutilised hormone which may be significant in respect of abnormal growth-stimulation, for breast and cervical cancer in women and prostatic cancer in men all tend to occur most frequently at or after the involutionary period in the life of these organs, when their functional response to the hormones is ceasing or has ceased.

Cancer of the Cervix

The evidence of Stocks, that the death-rate from cervical cancer—and in this connection the death-rate may be taken as a fair index of the incidence of cervical cancer—increases as we go down the social scale, introduces a new conception suggesting that some social factor or factors must be at work, and the influence of fertility at once presents itself as a possible explanation.

Böhmert[7] has produced figures of the cancer death-rates in large cities of different countries, which show that three countries have the highest proportional incidence of uterine cancer and the lowest proportional incidence of breast cancer, and these are, or were, all countries with a particularly high birth-rate. In this country the unhappy fact that the reproductive rate is in inverse ratio to the social

scale might well be held to explain the increase in cervical cancer as we go down the scale, but Stocks's analysis shows that this is not borne out by the figures. What one finds in gynæcological practice is that it is parity but not necessarily multiparity which is so often recorded in the history of women with cervical cancer. The mother of one or two children is as liable to cancer of the cervix as the mother of a dozen.

Indeed the statistical investigation of the incidence of cancer of the cervix as between parous and nulliparous women does not bear out the general impression that it is so vastly more common in parous women, when the relative proportions of the parous and nulliparous groups in the cancerous period of life are taken into consideration. I cannot give you precise figures of these categories in Scotland, but, from information given me by the Registrar-General, I conclude that in the cancer period of life (from 40 to 70 years of age), close on 80 per cent. of women are married or widows and probably 68 per cent. parous. Fertility of itself is therefore not the outstandingly dominant factor which it has so often been taken to be.

Another general impression to which most gynæcologists would probably subscribe is that cervical cancer is etiologically related to long-standing chronic cervical infections with or without associated lacerations dating from childbirth or some imperfect operative procedure. A great deal of evidence has been brought forward in support of it. In Italy, Bossi is stated to have followed up for an unspecified period of years 1000 women who had been treated surgically for chronic cervicitis without finding a single case of subsequent cervical cancer. In America figures have been collected [8] of more than 18,000 women who might be regarded as having had adequate treatment for chronic cervicitis, and amongst these only 15 were stated to have developed cervical cancer subsequently. On the other hand, of 2555 women with cancer of the cervix, only 33 had had adequate treatment for pre-existing cervical lesions.

Now the validity of such statistics depends on the accuracy of the follow-up of the cases, and upon whether a sufficiently long interval —say ten to fifteen or twenty years—has been allowed to elapse before deductions are drawn. Thus Pemberton and Smith, who were responsible in 1929 for some 5000 of the 18,000 cases quoted above as to the apparent prophylactic value of adequate treatment of cervical infections and lacerations, had to admit some years later that their follow-up had not been sufficiently accurate. Pemberton's corrected figures [9] increased his estimate of the subsequent occurrence of cervical cancer in women whose cervices had been adequately treated from 1 in 1000 to 1 in 78, or including some dubious cases, to 1 in 58. Pemberton therefore recanted his opinion that trachelorrhaphy was a preventive of cervical cancer, and his frank avowal cannot fail to shake one's confidence in the accuracy of other similar statistics.

If, however, we assume for the sake of argument the substantial

accuracy of most of these figures we may link them up with the increasing incidence of cancer of the cervix as we go down the social scale, for in gynæcological practice we see many more cases of cancer of the cervix in hospital than in private, even allowing for the greater relative number of our hospital patients. Since fertility cannot explain this, we are driven to associate it with the probabilities that the poorer women have hitherto received less careful attention in childbirth with the consequence of more cervical injuries, and have been less disposed to seek or less able to obtain adequate treatment for cervical infections. For while the theory that long-standing irritation *per se* can cause cancer is no longer accepted, that does not affect the view that, given the presence of some unknown predisposing cause of cancer, such irritation may be the more immediate cause. It is in this rôle that we may regard the leucorrhœa of the woman with chronic cervicitis. J. J. M. Shaw pointed out that in experimental cancer a carcinogenic irritant acts best if it is applied to the surface over a prolonged period in a viscous solution, and these are the very conditions present in the woman with a chronic infection of her cervix.

Whatever mental reservations one may have as to the precise preventive value of the adequate treatment of cervical infections and lacerations in relation to cancer, the general observance of this practice by gynæcologists is not likely to diminish, because there is abundant clinical evidence to show that the infected cervix may act as a septic focus and give rise to chronic pelvic pain as well as to other symptoms of an almost protean variety. Indeed, to do justice to this one point a whole lecture might well be devoted.

If better obstetrics, greater care in curing chronic cervical infections and the repair of lacerations comprise all that can be suggested for the prevention of cancer of the cervix, there still remain two points to be mentioned which would help to reduce the devastating effects of the disease by increasing the number of early diagnoses. One is to educate our middle-aged and elderly patients to have a yearly or even six-monthly examination of the pelvis in the same way as so many persons have a six-monthly dental examination. The detection of a very early cervical cancer is often a matter of some difficulty, and such examinations would have to be made by gynæcologists, or by general practitioners who had had some special training in the subject. If this suggestion be regarded as a counsel of perfection, the same cannot be said of educative propaganda amongst women as to the significance of the early symptoms of the disease. It is one of the tragic features of it that these early symptoms, slight intermenstrual bleeding and leucorrhœa, are so commonplace that many women disregard them until the disease is far advanced. The danger of creating a widespread cancer-phobia by such propaganda is not so serious as the continuance of an avoidable high mortality from the disease. The intention of such propaganda is, as I think Lord Moynihan said, " not to scare people to death but to frighten them into life."

In conclusion, there are two other forms of cancer seen by the gynæcologist in regard to which something may usefully be said as to prevention—namely, cancer of the ovaries and cancer of the vulva.

I think that most gynæcologists will agree that many of the malignant ovarian cysts that we see in the operating theatre were probably benign to start with. From the strictly pathological standpoint even this guarded statement may perhaps be open to challenge, but I shall not delay to discuss that. My point is that for this reason every ovarian tumour should be removed as soon as possible after its presence is recognised. There are other good reasons also which make that an axiom of gynæcological teaching, but it requires to be said when we are considering the prevention of cancer.

Stocks has shown in his survey that those regions in England and Wales which have a high mortality from cancer of the ovaries have a rather low mortality from uterine and other forms of cancer. Perhaps the speed with which secondary cancer of the ovary develops in comparison with a possibly small and silent primary focus in the breast or alimentary canal, and the way in which the secondary ovarian growth early and completely dominates the clinical picture, may vitiate the accuracy of the death-rate attributed to ovarian cancer, but such precision in registration is not to be expected except as the result of careful post-mortem examination. Stocks also found that the death-rate of ovarian cancer is like that of breast cancer in two respects—first, that it is higher in each age group amongst single women than amongst married women and widows, and secondly that it diminishes steadily as the social scale drops, being in this respect in direct contrast to the cervical cancer death-rate. It is difficult to resist the speculation put forward by Stocks that this parallelism between ovarian and breast cancer must somehow be linked up to the influence of œstrogenic hormones in cancer-susceptible persons.

Cancer of the vulva is less often encountered than cancer of the uterus or ovaries, but it is a peculiarly distressing and very fatal disease. There is, however, no form of gynæcological cancer in regard to which there is more obvious scope for prevention, because in many cases it arises out of a pre-existing leucoplakia of the vulva. This fact is familiar to all gynæcologists, but Taussig, who has made a special study of the point, maintains that no less than 50 per cent. of all cases of vulval cancer originate in this way. Now leucoplakia of the vulva is associated with such intense and distressing pruritus that few patients are likely to tolerate it for long without seeking medical advice, and it is so obvious on inspection that few doctors are likely to miss it. The danger is that time may be wasted in unavailing attempts to cure the condition by soothing applications. When the disease has reached the second or subsequent stages, or even in the earlier stages has not shown any improvement under a short term of medical treatment, an excision of the whole vulva is clearly indicated

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I would end this imperfect survey of the part which obstetricians and gynæcologists are playing in the prevention of chronic disease and cancer by asking a question. If we place all the time, energy, thought and care that are being expended in the ways I have mentioned on one side of a balance-sheet, have we an adequate return in terms of positive prevention to place on the other? I am afraid that the answer is "No," and I am not aware of any aspect of medicine in which it is or can well be otherwise. Only a small proportion of the ills to which flesh is heir can be prevented by purely medical methods. More is to be expected from a general raising of the standard of living such as may well follow on better nutrition, better housing and social security effected on a national scale. If we can believe our politicians, these much-needed improvements await us in the post-war world.

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TRAUMATIC ULNAR NEURITIS

THE RESULTS OF ANTERIOR TRANSPOSITION OF THE ULNAR NERVE *

By R. L. RICHARDS, M.D.

IN the groove behind the medial epicondyle of the humerus the ulnar nerve is in a position of unusual vulnerability. It is particularly liable to be damaged as the result, either immediate or late, of fractures in the neighbourhood of the elbow-joint; and traumatic ulnar neuritis is one of the more common peripheral nerve lesions encountered in civil surgery. This paper deals with the results in 26 cases treated by operation at a Peripheral Nerve Injuries Unit between September 1941 and March 1944; the series includes all cases except gunshot wounds or other direct injuries of the nerve, and the cases are summarised in the Table. The majority of the patients (20 out of 26) were members of H.M. Forces. Their ages ranged from 19 to 53 years, with an average of 33 years. In 12 cases the right arm was affected, in 14 cases the left.

CLASSIFICATION

Platt (1926) described three clinical groups:—(1) Ulnar nerve lesions associated with recent fractures of the lower end of the humerus; (2) late involvement of the ulnar nerve after fractures in the region of the elbow (tardy ulnar palsy); and (3) recurrent dislocation of the ulnar nerve. To these the following additional groups may be added:—(4) ulnar nerve lesions associated with arthritis of the elbow, without any history of previous trauma; (5) lesions associated with congenital cubitus valgus; (6) lesions resulting from occupational pressure upon the ulnar nerve; and (7) injuries near the nerve. The present series does not contain any case in which the nerve lesion resulted from a recent fracture. The cases have been grouped as follows.

1. *Tardy Ulnar Palsy* (Cases 1-15).—The lesion which is most frequently associated with the development of tardy ulnar palsy is a fracture of the lower end of the humerus sustained in childhood, in which a fragment consisting of the lateral humeral condyle remains ununited; later cubitus valgus develops (Figs. 1 and 2). Seven of the 15 cases of tardy ulnar palsy had sustained fractures of this type. The majority of these patients had an elbow-joint which, although greatly distorted, was functionally little short of normal. Two patients had old ununited fractures of the medial epicondyle (Fig. 3). Two had old fractures of the head of the radius, and in one of these the

* From a Peripheral Nerve Injuries Unit in an Emergency Medical Service Hospital, Scotland.

head of the bone had been removed elsewhere. In the remaining 4 cases, when the patient came under observation the elbow was so arthritic that it was impossible to decide the nature of the original fracture. Platt (1926) states that in 75 per cent. of the recorded cases of tardy ulnar palsy the interval between the initial injury and the onset of symptoms referable to the ulnar nerve is not less than 10 years; in his own cases the longest interval was 51 years. In the present series the interval varied from 18 months to 44 years, with an average of 14·6 years.

2. *Arthritis of the Elbow* (Cases 16-20).—One of the cases in this group (Case 16) might have been included in the previous group; after a latent period of 11 years, a tuberculous infection of the left elbow-joint was followed by ulnar neuritis. In the remaining cases there was clinical and radiological evidence of arthritis of the elbow-joint without any history of previous trauma (Fig. 4). The neuritis associated with arthritis of the elbow-joint appears to be more severe and to develop more rapidly than that which follows fracture of the humerus or pressure upon the nerve.

3. *Recurrent Dislocation* (Cases 21 and 22).—Recurrent dislocation of the ulnar nerve may occur in those who have an abnormally shallow ulnar groove, associated with a mild degree of congenital cubitus valgus and hyperextensibility of the elbow-joint. Repeated dislocation of the nerve may occur almost unnoticed until the symptoms of ulnar neuritis develop in late middle life. The condition is often hereditary and, although bilateral, in a right-handed person symptoms usually appear first in the right arm. Occasionally injury in the region of the medial epicondyle may cause sudden dislocation of the nerve followed by persistent symptoms (Case 21).

4. *Occupational Pressure* (Cases 23-25).—This group is closely related to the preceding. The depth of the ulnar groove and the mobility of the ulnar nerve vary considerably; in a shallow groove a relatively fixed nerve may be subjected to prolonged pressure as the result of an habitual posture of the limb. Harris (1943) has described cases in which ulnar palsy developed as the result of pressure of the elbows on a work-bench with an edge upturned like that of a tea-tray. In the present series, the 3 patients in this group were all in the habit of spending hours at a telephone, with the left elbow resting upon the edge of a table.

5. *Local Sepsis* (Case 26).—In the remaining case the neuritis was the result of an injury in the neighbourhood of the medial epicondyle. A rusty nail was driven into the arm and cellulitis followed; when this resolved, ulnar neuritis persisted.

Clinical Features

Whatever the predisposing cause, the clinical features of the ulnar neuritis are the same. In the majority of cases they develop insidiously, and may have been present for months or even years before the patient

seeks medical advice. Not infrequently a minor injury in the region of the medial epicondyle is the precipitating factor which draws the patient's attention to his lesion. In the present series the duration of symptoms before the patient was admitted to hospital varied from 4 days to 7 years.

TABLE

Case No.	Age in Years.	Arm.	Original Lesion.	Latent Period.	Duration of Symptoms.	Subjective.						Objective.				
						T.	P.	N.	Wa.	We.	C.	Wa.	We.	Par.	Hy.	S.L.
1	21	L.	Fracture internal condyle of humerus	18 months	6 months	−	+	+	−	−	+	+	+	−	−	+
2	39	L.	Old fracture of elbow with cubitus valgus	3 years	1 year	+	−	+	−	−	−	−	+	−	+	−
3	32	R.	Old fracture both epicondyles and olecranon	4 years	1 year	+	−	−	+	+	+	+	+	−	+	−
4	10	L.	Old fracture of lower end of humerus: cubitus valgus	6 years	5 months	+	−	+	−	−	+	−	−	−	+	−
5	33	L.	Fracture head of radius with cubitus valgus	8 years	7 years	+	−	+	−	−	−	−	+	−	−	−
6	30	L.	Fracture lateral epicondyle: cubitus valgus	9 years	6 months	+	−	+	+	+	−	+	+	—	—	+
7	23	R.	Ununited fracture medial epicondyle	10 years	18 months	+	−	+	−	+	−	−	+	−	+	−
8	19	R.	Fracture lateral condyle of humerus	10 years	2 years	+	−	+	−	−	+	−	+	−	+	−
9	25	L.	Old elbow injury with osteo-arthritis	13 years	14 months	−	+	−	−	+	+	+	+	−	−	+
10	21	R.	Ununited fracture of lateral condyle	14 years	4·5 months	+	−	+	−	−	+	−	+	−	−	+
11	20	R.	Fracture neck of radius: head excised	15 years	1 month	−	−	+	−	−	−	−	−	−	−	−
12	31	R.	Old supracondylar fracture of humerus	24-26 years	1 month	+	−	+	−	+	−	+	−	−	+	−
13	37	R.	Old fracture lower end of humerus	30 years	7 months	+	−	+	−	−	+	+	−	−	+	−
14	36	R.	Ununited fracture of lateral condyle: cubitus valgus	30 years	2 years	−	−	−	+	+	+	+	+	−	+	−
15	53	R.	Old fracture: osteo-arthritis of elbow: cubitus varus	44 years	6 months	+	−	+	+	+	+	+	+	−	+	−
16	28	L.	Tubercle of elbow	11 years	9 months	+	−	+	+	+	+	+	+	−	−	+
17	53	L.	Arthritis of elbow	...	6 months	+	−	−	−	+	−	+	−	−	−	+
18	32	R.	Arthritis of elbow	...	18 months	−	−	+	+	+	+	+	+	−	−	+
19	39	R.	Arthritis of elbow	...	2 years	+	−	+	+	+	−	+	−	+	−	+
20	44	R.	Arthritis of elbow	...	1 month	+	−	+	−	−	+	+	+	−	+	+
21	26	L.	Dislocated nerve	...	4 days	+	+	−	−	−	−	−	−	−	−	−
22	49	L.	Congenital cubitus valgus: recurrent dislocation	...	4 months	−	+	−	−	+	−	+	+	−	−	−
23	40	L.	Slight congenital cubitus valgus; pressure upon nerve	...	9 weeks	+	−	+	−	+	−	+	+	−	−	+
24	37	L.	Pressure upon nerve	...	4 months	+	−	+	+	−	−	+	+	−	−	+
25	35	L.	Pressure upon nerve	...	3 months	+	−	+	+	+	−	+	+	−	+	−
26	51	L.	Injury followed by cellulitis	...	2 years	+	−	−	−	+	−	−	−	−	+	−

T = Tingling
P = Pain
N = Numbness

Wa = Wasting
We = Weakness
C = Affected by cold

The symptoms may be either sensory or motor, or both. The most common complaints are tingling (20 cases) and/or numbness (19 cases) in the sensory distribution of the ulnar nerve. Weakness of the affected hand is also a common complaint (15 cases). The weakness is frequently described as general weakness of the limb, and in cases of tardy ulnar palsy the patient may complain that his grip is poor and that he is unable to lift heavy weights. This disability appears to be the combined result of the old bony injury and the weakness of the hand. More intelligent patients complain of difficulty in perform-

ing fine movements, *e.g.* one patient (Case 14) stated that for many years he had been unable to write legibly, and always used a typewriter. Wasting of the intrinsic muscles of the hand was noted by only 9 patients, although objective evidence of wasting was present in 17.

TABLE

Condition of Nerve.	Immediate Result.	Late Result.	Damage to Medial Cutaneous Nerve.	Disposal.	Complications.
ıdherent and in scar	Improved	...	Nil	To Con. Depot	Spasm of biceps
ıdherent and flattened	Improved	...	Nil	To Con. Depot	Stiff elbow
Slightly thickened	Marked improvement	2 4/12 years. Excellent	Nil	Work as engineer	Nil
Dislocated in front of groove and adherent	Improved	...	Nil	To Con. Depot	Nil
lard neuroma, adherent	Improved	...	Nil	To duty	Nil
ısiform adherent neuroma	I.S.Q.	2 years. Excellent	Slight	To Con. Depot	Swelling of elbow
Flattened, adherent and very vascular	Improved	...	Slight	To duty	Spasm of biceps
ijected and slightly adherent	Improved	...	Nil	To Con. Depot	Nil
ollen soft lateral neuroma	I.S.Q.	2 0/12 years. Ulnar, very good. Medial cutaneous, improved	Severe	Category E	Nil
bcutaneous in front of lbow : neuroma : kinked	I.S.Q.	3 months. Still I.S.Q.	Slight	To duty	? Functional
ıormal		...	Slight	To unit	Nil
Flattened :	I.S.Q.	...	Slight	To duty	Nil
adherent œdematous :	Marked improvement	1 4/12 years. I.S.Q.	Slight	To Con. Depot	Painful elbow
Flattened : adherent : acutely angulated	Improved	6 months. Still improving	Nil	To duty	Nil
oft, flat neuroma	Slight improvement	10/12 years. Improved	Nil	To duty (policeman)	Nil
oft neuroma : not adherent	Improved	6 months. Still improving	Nil	To duty	Nil
ɔft, fusiform neuroma	I.S.Q.	...	Nil	To work as boilerman	Nil
Adherent : thickened : constricted	Marked improvement	1½ years. Slight improvement	Nil	To Con. Depot	Nil
Slightly swollen : adherent	I.S.Q.	10/12 years. Excellent	Slight	Category E (shepherd)	Nil
Firm neuroma	I.S.Q.	...	Nil	To work (bus-driver)	Nil
Thickened : adherent	Improved	8/12 years. Improved	Nil	To duty	Sepsis + + +
ɔver epicondyle : slight neuroma	Improved	...	Nil	To work (Post Office)	Nil
Adherent : injected	I.S.Q.	...	Slight	To duty	Nil
Slightly thickened	Slight improvement	6 months. Still I.S.Q.	Nil	To Con. Depot	Nil
Neuroma *distal* to ulnar groove	I.S.Q.	2 years. Excellent	Slight	Category E	Primary atypical pneumonia
Normal	I.S.Q.			Did not return to work	Functional
Slightly scarred	Improved				

Par = Paralysis
Hy = Hypæsthesia and/or Hypalgesia
S.L. = Sensory Loss
Vm = Vasomotor Disturbance
Sm = Sudomotor Disturbance

Pain of ulnar distribution is a rare complaint (4 of the 26 cases). Approximately half the patients complained either that the affected hand was colder than its fellow, or that exposure to cold aggravated their symptoms. All the patients were questioned about sweating, but only 1 (Case 9) complained of execssive sweating in the affected hand.

Objective findings are those of ulnar palsy of varying degrees of severity. Wasting and weakness of the muscles innervated by the ulnar nerve are observed in a high proportion of cases, but it is rare for the condition to cause total paralysis in any one muscle. The wasting

usually appears first in the muscles supplied by the terminal branches of the nerve, *i.e.* the first dorsal interosseous and the adductor pollicis (Figs. 5 and 6). Another early sign is that when the hands are at rest the little finger tends to drift away from the other digits, and to be held in slight flexion (Fig. 6). The majority of cases (22 out of 26) show objective evidence of interference with the function of sensory nerve fibres. In mild cases there is hypæsthesia and hypalgesia, with impairment of two-point discrimination; but all gradations may be observed from this to complete loss of all modalities of sensation in the autonomous territory of the ulnar nerve. Vasomotor disorders are found in a minority of cases; there may be cyanosis and coldness of the little finger and hypothenar area. Sometimes the whole hand is objectively colder than the normal hand. Elsewhere it has been shown that in this type of nerve lesion, reflex vasomotor responses in the little finger are unaffected (Richards, 1944). In one case (Case 9) spontaneous excessive sweating was observed in the territory of the ulnar nerve; in the remainder sweat secretion was clinically normal.

Medial Cutaneous Nerve of the Forearm.—The medial cutaneous nerve of the forearm divides in the arm and its anterior and posterior divisions pass distally in front of the medial epicondyle. There is considerable variation in the exact position of the branches, but one or other is usually encountered during the operation of anterior transposition of the ulnar nerve. Not infrequently the posterior branch is found to pass directly over the prominence of the medial epicondyle, and pressure upon the nerve in this position may account for the pre-operative finding of diminished sensation over the inner side of the forearm in some cases of ulnar neuritis.

Treatment

All the cases were operated upon, the ulnar nerve being transposed to the front of the elbow. Details of the operative technique have been described elsewhere (Learmonth, 1942). The incision passes behind the medial epicondyle, the ulnar nerve is freed from its groove and, after division of the flexor-pronator muscle group, placed deep to these muscles beside the median nerve. Twenty-four of the cases have had this operation performed. The two exceptions (Cases 15 and 16) were the original cases in the series, and were operated upon before the present technique was devised, by the method described by Sir Harold Stiles (1922).

After operation the affected limb is usually kept in plaster for 3 weeks, with the elbow flexed to 90°. Thereafter active movement is encouraged, and 10-14 days later the patient may leave hospital.

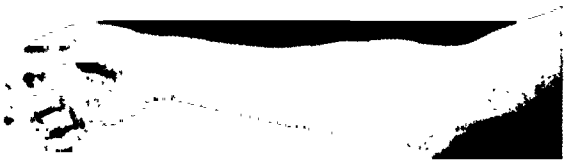

FIG. 1.—Case 10. Photograph to show cubitus valgus and scar of operative incision passing in front of medial epicondyle.

FIG. 2.—Case 10. Radiograph to show ununited fracture of lateral humeral condyle and distortion of elbow-joint.

FIG. 3.—Case 7. Radiograph to show ununited fracture of medial epicondyle.

FIG. 4.—Case 19. Radiograph to show arthritis of elbow without history of previous trauma.

FIG. 5.—Case 18. Photograph to show wasting of right first dorsal interosseous muscle.

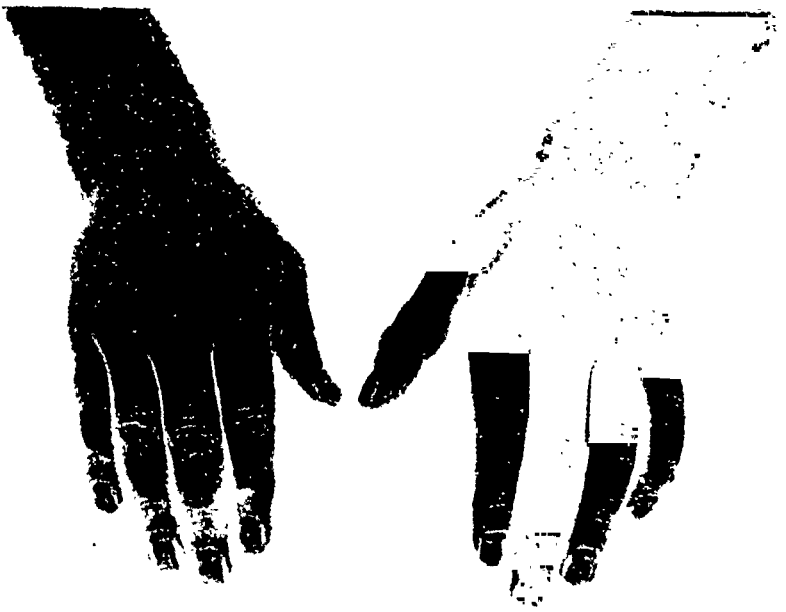

FIG. 6.—Case 24. Photograph to show wasting of interossei and slight flexion and abduction of little finger.

Surgical Pathology

Since the operation notes have been written by several assistants, a certain lack of uniformity in the description of the nerve is inevitable. In 10 cases the presence of a neuroma is mentioned, in 14 the nerve is recorded as abnormal in some respect (adherent, kinked, inflamed, etc.), and in only 2 cases was the external appearance of the nerve considered to be normal. These findings indicate that the presence of a neuroma is not a necessary accompaniment of symptoms referable to the nerve, and the term "traumatic ulnar neuritis" is probably as accurate as the alternative "traumatic ulnar neuroma" suggested by Riddoch. In the present series there is no correlation between the presence of an actual neuroma and either the duration or the severity of symptoms. Two patients had had a previous operation upon the nerve.

Case 10.—L. H., age 21 years, sustained an injury to the right elbow at the age of seven. At the age of twelve he developed typical symptoms of ulnar neuritis, and anterior transposition of the nerve was performed. This relieved his symptoms until he joined the army. After five months' training he again developed symptoms of ulnar neuritis. The nature of his fracture and the state of his arm are shown in Figs. 1 and 2. An operation scar was present anterior to the medial epicondyle, and the ulnar nerve was palpable lying subcutaneously deep to the scar. At the second operation the nerve was found in a tunnel of subcutaneous tissue. It was swollen into a fusiform neuroma, and was acutely angulated at both ends of its abnormal course, at the upper end over the medial intermuscular septum and at the lower end over the fascia between the two heads of flexor carpi ulnaris. The septum and fascia were excised, and the nerve was placed deep to the flexor-pronator origin. This relieved the symptoms referable to the ulnar nerve, but later he had trouble from hyperæsthesia in the distribution of the medial cutaneous nerve of the forearm. More than two years after operation he has "little if any sensory or motor disturbance of the ulnar distribution," but "marked sensitivity in the region of the medial epicondyle posteriorly." *

Case 9.—B. R., age 25 years, fractured his left arm at the age of twelve. Apart from the initial symptoms due to the fracture, he had no complaints until fourteen months before admission. He then developed "burning pain" down the inner side of the left forearm and in the 4th and 5th digits. Four months previous to admission to this unit, an operation on the nerve had been performed elsewhere, which did not relieve his symptoms. In view of the severity of his symptoms the nerve was re-explored; it was found to be within the groove, where it was densely adherent and swollen to form a very firm lateral neuroma. The nerve was transposed and placed deep

* I am indebted to Major G. D. Rowley, R.A.M.C., for this report.

to the flexor-pronator muscles. The immediate result of the operation was disappointing.

These two cases illustrate the importance of attention to certain technical details in the operation :—(1) Adequate mobilisation of the nerve above and below the epicondyle ; (2) excision of the medial intermuscular septum and, if need be, the fascia in the flexor-pronator muscles ; and (3) placement of the nerve preferably in a natural intermuscular plane.

Results

At the time of discharge from hospital, an assessment of the immediate result is made. In the majority of cases the immediate result is most gratifying. Although there are no available statistics, undoubtedly the chief improvement is diminution in the amount of tingling. At the time of discharge from hospital, 16 patients stated that there was a definite improvement in their condition, while the remainder, although unwilling to admit of immediate improvement, agreed that they were certainly no worse. At this time objective signs of improvement are not apparent. A complication which has been observed in some cases is a tendency for spasm of the biceps to restrict extension of the elbow ; this can usually be overcome by encouragement and active exercises. Operative interference with the branches of the medial cutaneous nerve may result in a very unpleasant hyperæsthesia over the inner side of the forearm. This is particularly liable to happen when an incision passing in front of the medial epicondyle is used (see Case 10 above). It was for this reason that a posterior incision (Fig. 7) was used in the present series. All patients have been questioned regarding hyperæsthesia, and the forearm has been carefully tested for any disturbance of sensation in the territory of the medial cutaneous nerve. With the exception of Case 10, none of the patients complained of hyperæsthesia, but several on direct questioning mentioned numbness over the point of the elbow. When sensation is tested after operation, a small area of anæsthesia over the olecranon and posterior to the distal portion of the scar of the operation wound is frequently found, but this does not constitute a severe disability. A scar passing behind the medial epicondyle is not subject to pressure when the elbow is resting upon the edge of a table or similar structure.

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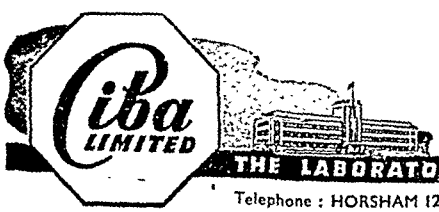

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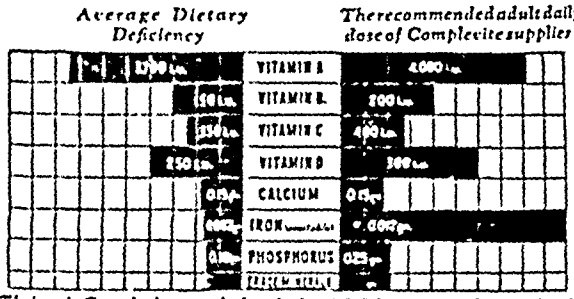

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neuritis but hyperæsthesia in the territory of the medial cutaneous nerve of the forearm. There is no doubt that the best results are obtained in those patients who are operated upon shortly after the onset of symptoms; patients with a long history do not do so well. The general statement that a patient will regain what he has lost in the previous year is probably true only when applied to the early case of traumatic ulnar neuritis. Of the 20 Service patients, 9 are known to have returned to some form of duty, 8 were discharged to

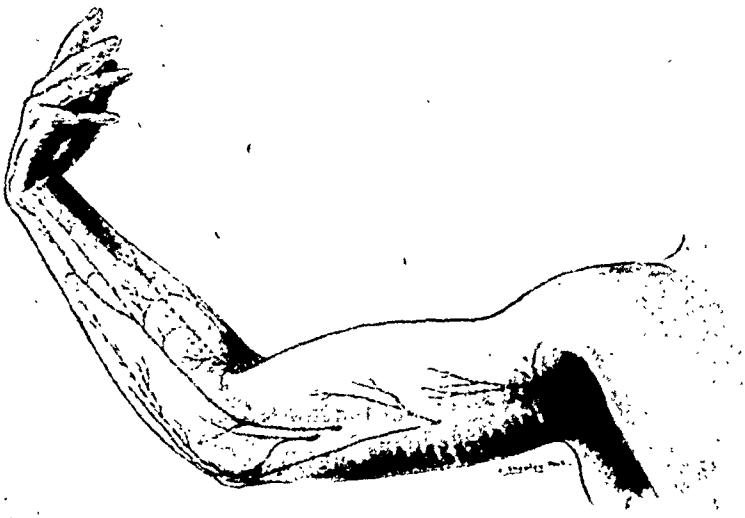

FIG. 7.—Drawing to show position of cutaneous nerves and site of incision for anterior transposition of ulnar nerve.

Army Convalescent Depots and their disposal thereafter is uncertain, and 3 were discharged as physically unfit for any form of military service. The 6 civilians, with one exception, returned to their former employment.

SUMMARY

If correctly performed, anterior transposition of the ulnar nerve is a satisfactory operation for traumatic ulnar neuritis. Immediate subjective improvement may be expected. The late results are more variable, and vary with the duration of symptoms before operation. At best the patient may expect to regain what he has lost in the previous year, at worst the progress of his lesion will be arrested.

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6. *Shortening of Clotting Time.*—Smith and Hale,[8] working with cocci-free broth filtrates which contained the enzyme, have shown that by the addition of up to 10 per cent. of an activating substance—produced by preparing a 10 per cent. extract of ground human or rabbit testicle in distilled water—they could appreciably shorten the clotting time of "atypical" human plasma or slowly working plasma from various animal species. We have tried this testicle extract in a small series of tests, adding 0·05 or 0·01 c.c. to 0·5 c.c. of plasma and have found it to shorten the clotting time in some cases. In preliminary tests no appreciable advantage was obtained by this enriched plasma for the slide agglutination. As we observed spontaneous clotting in a case of deteriorated plasma after addition of this extract, the necessity of always putting up controls is emphasised.

7. *Sterility of Glassware, and Contaminating Organisms*—The use of sterile test-tubes for the coagulase test in order to avoid false positives has been advocated.[19] This, in our experience, is not strictly necessary. False negative results, however, can be obtained when the culture used for inoculation includes also *B. proteus* or fibrinolytic streptococci (of Group A or C). These organisms will readily destroy any clot present (if added afterwards), or prevent clot formation, if present from the start of the test. Of a great variety of organisms tested no other appeared to have coagulative powers.

8. *Comparison of Cultures on Solid and in Fluid Media.*—In our experience either of these methods may be used, with similar results. We prefer culture on solid medium, but trypsin broth cultures are also very good, probably due to a more luxuriant growth if compared with other fluid cultures. Plasma diluted with broth is in general not superior to saline dilutions.

9. *Length of Incubation.*—On the whole, overnight incubation at 37° C. seems preferable to 3 hours' water-bath incubation and subsequent standing at room temperature, though the difference is slight. One point in favour of the latter method is the fact that in a very few instances, using overnight incubation in the water-bath, a partial dissolution of the clot was observed. This process should be distinguished from a retractible clot which is mainly seen when using higher dilutions of plasma.

Slide Agglutination.—The clumping of staphylococci in the presence of plasma was noted in 1908,[4] and its use for routine purposes was recommended by Birch-Hirschfeld in 1924, and recently by Cadness-Graves *et al.* in this country. We have not been as fortunate as some workers, who recorded a correlation of 100 per cent. between this and the coagulase test, having obtained, as will be shown below, false negative as well as positive results. Another and more disturbing feature was the phenomenon that in a few instances an obvious aureus strain failed to be clumped at first attempt, while a second test gave a positive result, using the same (fresh) human plasma and the same culture in approximately the same proportions. Only the latter result

has been recorded, thus reducing—perhaps unjustifiably—the numbers of false negatives. It should be remembered that according to some authors[6, 20] pathogenic strains split off coagulase negative variants. If the slide test is carried out with only one colony, it should be repeated in cases where the outcome is questionable.

Technique of Tests Used

Biochemical Examination

The carbohydrates were used in 1 per cent. peptone water solutions, inoculated with a loopful of a 24 hours' growth on agar or Löffler slopes, and incubated at 37° C. for 48 hours. This time limit was taken as it has been observed that some pathogenic strains were somewhat slow in fermenting mannite and other sugars, whereas some saprophytic strains will ferment mannite after further incubation[12, 21]. Gelatin stab cultures were also made and left at room temperature for eight weeks.

Coagulase Test

One half c.c. of neat human plasma (fresh, or dried and diluted with distilled water), or occasionally a 1 : 2 saline dilution of plasma was inoculated with a loopful of culture on solid medium. The tubes were incubated at 37° C., readings being made at frequent intervals, the last after 18 to 24 hours.

Slide Agglutination

A drop of saline and a drop of plasma were placed on a glass slide. A loopful of culture or one colony was then taken up with the platinum loop and approximately the same quantity of growth was deposited next to each drop. The fluids were then brought into contact with the cocci while stirring for about a dozen times. Unless the growth was of an R type, the saline suspension remained smooth and even, whereas in the case of virulent staphylococci the plasma prevented the formation of a smooth suspension, or caused clumping after an interval of up to 15 seconds. Avirulent strains yielded as even a suspension with plasma as with saline.

Results

As indicated above, 200 aureus and 125 albus strains were examined. Fourteen aureus strains proved to be coagulase negative, which fact tallied in most cases with the outcome of slide agglutination and fermentation tests. Twenty-five albus strains were found to be coagulase positive.

As Table I shows, the aureus and coagulase positive albus strains fermented in most instances lactose, mannite, trehalose and sorbite, whereas coagulase negative albus strains did so to a very much lesser degree. The difference is particularly great with mannite, but sorbite also proved of value, as only a quarter of the albus strains were able to ferment this sugar. Gelatin was liquefied by the latter in about a third of the cases. It is a point of interest that the coagulase negative

aureus strains showed a less marked difference, as they were able to use the various sugars in 40 to 60 per cent. The citreus strains—not tabulated—were found to have varying fermentation properties, but

TABLE I

Positive Results obtained with the Following Media

Groups.	Number examined.	Glucose.	Lactose.	Mannite.	Gelatin.	Trehalose.	Sorbite.
Coagulase positive aureus	186	186 100%	184 98·9%	184 98·9%	184 98·9%	99 of 107 92·5%	74 of 82 90·2%
Coagulase positive albus	25	25 100%	25 100%	24 96%	24 96%	15 of 15 100%	15 of 15 100%
Coagulase negative albus	100	87 87%	64 64%	18 18%	35 35%	25 of 56 44·6%	13 of 50 26%
Coagulase negative aureus	14	14 100%	9 64·3%	6 42·9%	6 42·9%	6 of 10 60%	5 of 8 62·5%

The positive results indicate fermentation of the sugars and liquefaction of gelatin.

none fermented mannite, most did not ferment any of the carbohydrates used ; all liquefied gelatin.

The same relation between coagulase positive and coagulase negative staphylococci becomes evident if one notes the number of sugars fermented. In Table II only lactose, mannite, trehalose and sorbite are considered. Thus 96 per cent. of the aureus strains and 93·5 per cent. of the coagulase positive albus strains fermented either 4 or 3 sugars.

TABLE II

Groups.	Number examined	Number of Carbohydrates fermented.				
		4	3	2	1	0
Coagulase positive aureus	77	63 82%	11 14%	3 4%	... ...	... ...
Coagulase positive albus	15	13 87%	1 6·5%	1 6·5%	... ...	... ...
Coagulase negative albus	58	4 6%	4 6%	11 20%	34 60	5 8
Coagulase negative aureus	7	1 13·5%	2 28·8%	2 28·8%	2 28·8%	... ...

In contrast to this, only 12 per cent. of the coagulase negative albus strains showed fermentation of 4 or 3 sugars ; probably this figure is really still smaller, the cause for the apparent increase being that several of the albus strains were isolated from urine. There exists some ground for supposing that the aureus as well as virulent

albus strains may lose their power of coagulase production in the urinary tract, though still being pathogenic to man. Nevertheless, the bulk of the albus strains, 80 per cent., fermented only one or two of the sugars, while 8 per cent. were unable to use even one. Though these are only group characteristics, they may be of some help in some cases in determining the virulence of an unknown staphylococcus strain.

On the whole, the slide agglutination tallied well with the coagulase test; but, as Table III shows, some discrepancies were observed. In the case of coagulase positive albus strains, however, false negatives

TABLE III

Discrepancies between the Slide Agglutination and Coagulase Test

Group.	False Positive Slide Agglutination.	False Negative Slide Agglutination.
Coagulase positive aureus .	...	5 (2·6%)
Coagulase positive albus .	...	7 (28%)
Coagulase negative albus .	3 (3%)	...
Coagulase negative aureus .	1 (7%)	...

amounted to as much as 28 per cent. The numbers tested were, of course, small. Whether this result is only a chance outcome, or whether it holds good as group characteristic for all albus variants, thereby indicating a loss in pathogenicity coupled with loss of pigment, only further investigation can prove. None of the *citreus* strains was clumped by plasma.

Submitting the outcome of the coagulase tests to further examination, some disputable results become apparent. It is a mistake, as some workers have done, to test only definite aureus strains from abscesses or, on the other hand, definite albus strains, for example, from the air. There are some strains which, in respect of their pathogenicity, stand somewhere in between. Though the coagulase test is the best guide which we possess as to the virulence of staphylococci, it is bound to fail sometimes. What interpretation has to be made, for example, in the case of a strain which readily ferments glucose, lactose, mannite, trehalose and sorbite, liquefies gelatin in a few days, gives a positive slide agglutination, but fails to clot fresh plasma? Two strains of this kind were obtained from sputum and one from blood culture. In cases of R strains, too, some questionable negative results were obtained.

Staphylococcal infections of the urinary tract merit some detailed consideration. Repeatedly strains were isolated which, judging by the signs and symptoms of the patient, the number of polymorphs and cocci in the centrifuged deposit of the urine, and the outcome of the

fermentation tests should be regarded as pathogenic, while both the coagulase test and the slide agglutination failed to give a positive result. Frequently those strains were also unpigmented. This should prove a fruitful field for further investigation.

In determining the relative importance of staphylococci isolated from the blood stream the coagulase test is obviously of great value. In this series among 48 strains there were 6 which showed golden pigmentation, but which by the coagulase test were shown to be presumably non-pathogenic. It should be remembered, however, that with these methods only an opinion can be given on the relative importance of an organism, as coagulase negative staphylococci have been shown to be the causative organism in cases of acute and subacute endocarditis.[22, 23, 21]

None of the *citreus* strains proved to be coagulase positive.

Summary and Conclusions

Three hundred and twenty-five strains of staphylococci, isolated from various sources, were examined. They were divided into 186 coagulase positive aureus, 25 coagulase positive albus, 100 coagulase negative albus and 14 coagulase negative aureus strains. The biochemical properties were investigated. If a strain ferments four or at least three of the carbohydrates used, the probability of its proving to be pathogenic is increased. The coagulase test was found to give reliable results in probably over 99 per cent.

The slide agglutination, while not without value for presumptive testing, is liable to yield false positive as well as false negative results.

Different methods of carrying out the coagulase test are discussed. Unfiltered human plasma, dried *in vacuo*, was found to be a reliable substitute for fresh plasma and could be stored at least for 14 months at 4° C.

The addition of testicle extract to plasma which proved to work slowly was found to be advantageous.

It is a pleasure to acknowledge the help received from Dr W. R. Logan, Bacteriologist to the Infirmary, during this investigation.

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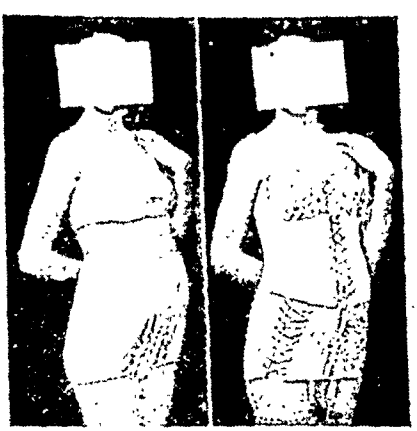

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THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS*

By D. M. DUNLOP, B.A., M.D., M.R.C.P., F.R.C.P.Ed.

THE treatment of thyrotoxicosis has advanced greatly during the last twenty years. Practically the only treatment before that time was rest, sedatives and the continuous administration of iodine, to which drug the patients soon became largely or completely refractory. It is true that many mild cases in young girls cleared up spontaneously on this regime, particularly if a satisfactory solution could be found to domestic worries, unhappiness at work or an affair of the heart. A proportion of more severe cases also eventually burnt themselves out after a greater or less number of years, during which their semi-invalid existence was a misery to themselves and their associates. A large number died from progressive heart failure with auricular fibrillation or in thyrotoxic crisis often precipitated by an infectious illness. Occasionally, after a physician had battled unsuccessfully with a patient for many years he would refer her practically *in extremis*, as a last desperate resort, to a surgeon. The result, which was almost invariably fatal, confirmed the physician in his complacent belief that surgery should play no part in this disease.

All this was changed when the proper pre-operative use of iodine was introduced by Plummer. This, combined with improved operative and, particularly, anæsthetic technique, reduced operative mortality in the hands of good surgeons to from 2 to 5 per cent. High mortality figures—approximately 12 per cent.—still occurred when late or neglected cases were referred for operation, or when the surgeon was unpractised in the art of goitre surgery.

The results of good medical and surgical co-operation in this sphere are as gratifying as any in the whole range of therapeutics. Improvement is usually dramatic within a few days of operation, and the total period of disability, from the pre-operative period till the patient is fit to return to work, averages from three to four months. The mortality over all is certainly under 5 per cent., and the recurrences after operation are probably not much more than 5 per cent.; the remaining 90 per cent. are rid once and for all of their disorder, though a few become myxœdematous—a condition readily amenable to simple treatment.

The last twenty years thus constitute a surgical era in the treatment of thyrotoxicosis in which the results have been infinitely superior to those of the purely conservative one which preceded it. Is the wheel

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 21st September 1944.

now going to complete a full circle and are we armed with new and potent drugs—about to start a new medical era which will in its turn supersede the surgical one?

Goitrogenic Substances

During the last few decades a number of agents have been described which would produce goitres. The effect of many of these substances was due to the alterations in iodine metabolism which they induced, since the simultaneous administration of iodine inhibited their goitrogenic action. Certain other substances such as cyanide induced goitres, presumably by inhibiting the biologic oxidation of the body cells. In 1928 it was first observed by Chesney and his co-workers [1, 2, 3] that rabbits fed on a diet of cabbage leaves tended to develop goitres, an observation confirmed by others and extended to include brassica seeds and soya beans as goitre-producing substances.[4, 5, 6, 7] The changes in the thyroid were described as those of a diffuse parenchymatous goitre involving hyperplasia and loss of colloid.*

These earlier accounts of goitrogenic substances differed as to whether the changes produced could be inhibited by the administration of iodine, as to the resulting metabolic state, and as to the nature of the effective mechanism, but they were the forerunners of the intensive studies which began to be made in 1941 by Kennedy, Griesbach and Purves,[9, 10, 11] who found that the feeding of brassica seeds not only produced goitres but that simultaneous changes occurred in the pituitary similar to those which follow thyroidectomy. Further, it was discovered that the hyperplasia of the thyroid did not take place after hypophysectomy, showing that the thyroid hyperplasia was mediated by the anterior pituitary.

In attempting a year later to find the causative factor in the rape seeds Kennedy [12] suggested that it might be a derivative of thiourea and indeed showed that the administration of allyl-thiourea caused the characteristic changes already noted in the thyroid and pituitary. His observation was slightly anticipated by Richter and Clisby [13, 14] and by the Mackenzies and McCollum,[15] who showed respectively that thyroid hyperplasia occurred on administering phenyl-thiourea and sulphaguanidine, an effect not influenced by adding iodide to the diet but which could be abolished by effective doses of thyroxine.

Subsequent studies by the Mackenzies [16] and by Astwood and his co-workers [17] have added the corner stone to our present knowledge on the subject from an experimental point of view. They showed that the hyperplasia of the acinar cells of the thyroid and the decrease in the colloid of the follicles which followed the administration of sulphonamides and of thiourea and its derivatives was associated with a fall in the B.M.R. which became marked after a few weeks, along with a decrease in growth and a diminished food intake. The apparently paradoxical finding was thus made that a hyperplastic thyroid could

be produced, similar to a thyrotoxic gland, but associated not with hyper- but with hypo-thyroidism.

The classical work of Marine,[18] however, has shown that the histological picture of thyroid hyperplasia and lack of colloid does not necessarily indicate thyrotoxicosis. It may mean that the thyroid is producing insufficient hormone for the needs of the body and is being stimulated to hyperplasia by the thyrotropic hormone of the pituitary to correct the deficiency. Such hyperplastic glands are often seen when there is an increased hormonal demand at puberty and pregnancy, during prolonged fevers such as tuberculosis and in people taking iodine-deficient diets. When iodine is given under such circumstances the thyroid reverts to its normal state. As we have seen, however, the giving of iodine had no effect on the hyperplastic glands produced by sulphonamides and thiourea and its derivatives, showing that the effect was due to some quite different action.

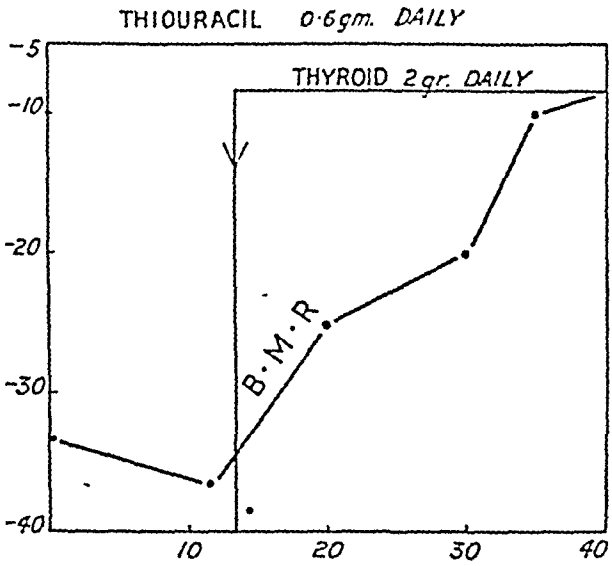


FIG. 1.—To show that thiouracil has no effect in neutralising the action of thyroid extract in a case of myxœdema.

Pharmacological Action.—The clinical association of thyroid hyperplasia and hypothyroidism might be explained on the basis that the goitrogenic agents neutralised thyroxine in the body tissues, the thyroid being again stimulated to hyperplasia by the thyrotropic hormone of the pituitary to correct the deficiency. The fact that the administration of thyroid extract or thyroxine entirely nullified the effect of the goitrogenic agents makes this explanation in turn untenable. This point was well illustrated by Williams and Bissell [19] who showed that thiouracil had no effect in diminishing the therapeutic potency of thyroid extract in two cases of myxœdema. I have treated one case of complete myxœdema with 0·6 gm. of thiouracil a day while simul-

taneously giving 2 gr. of thyroideum (B.P.) daily. The result is seen in Fig. 1 and shows that the effect of the thyroid on the B.M.R. was in no way diminished. Clinical improvement was also unimpaired.

These results suggest that the goitrogenic agents act directly on the thyroid, preventing the production of thyroid hormone. With a view to elucidating the chemical mechanism whereby these anti-thyroid substances work, Franklin, Chaikoff and Lerner [20] studied the effects of goitrogenic compounds on the *in vitro* conversion of radioactive inorganic iodide to thyroxine and diiodotyrosine by surviving thyroid slices. They found that thiourea and its derivatives strongly depressed this conversion. It is therefore thought that the action of thiourea derivatives is to interfere with the synthesis of thyroid hormone by preventing iodination of tyrosine. Since it is probable that these processes are enzymic in nature the effect of the anti-thyroid substances is probably anti-enzymic.

Our present knowledge derived from the foregoing experimental work may thus be summarised as follows: Thiourea derivatives → Prevention of iodination of tyrosine—Lack of thyroid hormone → Lowered metabolism—Compensatory increased production of thyrotropic factor—Thyroid hyperplasia.

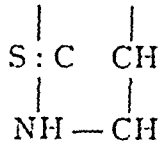
Clinical Application of Thiouracil.

Astwood [21] in 1943 was the first to put these experimental discoveries to clinical test. Thiouracil was given to three patients suffering from hyperthyroidism and to four with normal thyroid function. After a latent period there was a striking clinical improvement in the hyperthyroid patients with a significant fall in their basal metabolic rates between the ninth and sixteenth day. On discontinuing the drug after two months' treatment the symptoms of hyperthyroidism returned in about four weeks' time. One patient developed severe agranulocytosis with acute pharyngitis and a temperature of 105° after receiving 1 gm. daily for twenty-seven days and 2 gm. daily for six days. Recovery took place after an acute illness of some days' duration. The administration of thiouracil to the four patients with normal thyroid function had no effect after a month on their clinical condition or on their basal metabolic rates.

The latent period before any effect from thiouracil was noted corresponded with previous experimental observations in which it was observed that the lowering of metabolism coincided in time with the loss of detectable colloid from the thyroid. It is to be expected that the rate of metabolism will remain constant as long as the store of thyroid hormone in the gland is adequate to supply the organism. When the store becomes exhausted, the decreased rate of hormone synthesis becomes apparent. Since the store of thyroid hormone in hyperthyroid glands is greatly decreased it is not surprising that an effect is produced by thiouracil in thyrotoxic cases in as short a period

as ten to fourteen days. We know, however, that a normal person has a sufficient store of hormone to maintain the metabolism unchanged for from one to three months, which explains Astwood's negative results in normal subjects after a month's treatment.

Since Astwood's original clinical observations thiourea and its derivatives have been extensively used in therapeutics during the last year. Thiouracil



is now invariably employed in preference to thiourea as the latter has a disagreeable taste, and may produce vomiting, halitosis and conjunctivitis. Thiouracil is free from these objections and has been shown by Astwood [22] to be the most active of 106 chemical compounds which he tested for their inhibitory effect on thyroid function. Himsworth [23, 24] has made the fullest reports on the clinical use of the drug in this country, but I have collected the results of eight other observers in this country and America reporting on a total of 96 cases. I have myself used thiouracil for nearly a year in the treatment of 31 cases of thyrotoxicosis, and Professor Davidson has kindly allowed me to review eight other cases which he has observed for considerable periods of time.

No case has been included in this series in which the diagnosis was not absolutely clear. They were all classical in their signs and symptomatology, though differing considerably in their severity. Contrary to common belief the diagnosis of thyrotoxicosis is sometimes very difficult. Where a patient has a large nodular goitre and auricular fibrillation or a considerable primary goitre with all the classical symptoms and signs of exophthalmos, tachycardia, sweating, tremor and nervousness, the diagnosis is simple. In such cases organic endocrine disease is the main factor, since the patients can be cured by thyroidectomy, and the psycho-somatic factor is of less importance. At the other end of the scale is the patient without definite exophthalmos or goitre, but with sweating, tremor, exhaustion, tachycardia and psychological disturbances—suffering more from the effort syndrome than from thyrotoxicosis. Here psycho-somatic disturbances are maximal and the thyroid factor, if it exists at all, is minimal. There is no hard and fast dividing line between psycho-somatic disease of this nature and classical organic thyrotoxicosis, and it is very difficult to make a definite diagnosis in borderline cases. The B.M.R., sometimes endowed with almost mystical diagnostic powers by those with little experience of it is in reality often of little help as it is usually moderately raised in the effort-syndrome type of case. The therapeutic test, in which the effect of administering iodine is observed, is often of more value.

Dosage

As it appeared unlikely that the prevention of thyroxine synthesis was an all-or-nothing reaction it seemed probable that a relationship could be assumed between the dose of anti-thyroid substance and the degree of hypothyroidism produced. The aim was to decrease the synthesis of thyroxine to a normal level, but not below it, so that the pituitary would not be unduly stimulated to produce the indirect effect of thyroid hyperplasia.

Initial Dosage.—The few workers who had reported on the clinical use of thiouracil before I started to use it had employed it for initial treatment in doses varying from 0·6 to 2 gm. a day. The work of Williams and Bissell,[19] however, had shown that thiouracil was rapidly absorbed and rapidly excreted in the urine. After a single dose of 0·2 gm. the highest blood concentration of 2·3 mgm. per cent. was achieved in fifteen minutes. Thereafter it fell rapidly until at eight hours only traces of the drug were present. When 1·2 gm. were given daily it required twenty-four hours to reach a constant rate of excretion in the urine of about 300 mgm. a day and a constant concentration in the blood of 3 mgm. per cent. When 0·6 gm. was given a day it took forty-eight hours to attain this constant blood and urine equilibrium. Apart from the saving of twenty-four hours in producing a maximum concentration it seemed unlikely that 1·2 gm. would exert a greater effect than 0·6 gm. Thiouracil was therefore used in this latter dose for initial treatment, but on several occasions 1·2 gm. and even 2 gm. a day were given. In no case was any increased effect noted from giving these larger doses.

Maintenance Dosage.—All observers seem to be in agreement that a daily maintenance dose of 0·2 gm. is sufficient to maintain the effect once it has been produced by the initial treatment, and I have usually employed this maintenance dose, which has appeared to be entirely adequate since there has been no evidence of "escape" from the control of the drug when a reduction in dosage was made from 0·6 to 0·2 gm. a day. While it is possible, therefore, to be fairly dogmatic that these doses are entirely adequate for initial and maintenance treatment, there is yet insufficient evidence to show that this is the minimum dose required. I have lately used a smaller maintenance dose of 0·1 gm., as has Professor Davidson. From this limited experience I feel, like Himsworth,[24] that smaller maintenance doses than 0·2 gm. will prove adequate, and this may be of importance in avoiding certain toxic manifestations such as agranulocytosis, since all the drug in the blood exists in the cells, the concentration in the white cells being many times greater than in the red.

Results of Treatment

All the patients were weighed daily throughout their stay in hospital. An estimation of the B.M.R. and blood cholesterol was undertaken some three times a week. Frequent total and differential white blood counts were made. Apart from thiouracil the only medicine given was phenobarbitone in varying amounts according to the individual tolerance to the sedative, which varies greatly. Before starting the administration of thiouracil an attempt was made to procure the maximum benefit from rest in bed in hospital and sedative treatment. The drug was thus withheld until a base line had as far as possible been achieved as regards B.M.R., weight, pulse rate and blood pressure.

The effects of thiouracil were found to be on the whole extremely precise and predictable. For a few days no result was observed, but by the end of a week some subjective improvement occurred, the sweating and flushing of the skin being usually the first symptom to be ameliorated. Thereafter all the thyrotoxic symptoms steadily improved, the improvement being certainly not maximal at the end of a month when the patients usually left hospital, and being even more striking when they reported as out-patients subsequently. The patients have been observed for periods up to thirteen months. We are here concerned, however, more with the objective and measurable signs than with subjective improvement, and these also gave very significant results.

Fig. 2 is a composite picture of all the 31 cases showing the effect of thiouracil on their blood cholesterol concentration, weight and B.M.R. It will be seen that as the two former rise, the latter falls.

The Blood Cholesterol.—The blood cholesterol concentration is usually somewhat low in untreated hyperthyroidism—the average for the series being 140 mgm. per cent.—just as it is high in myxœdema. The concentration tends to rise as the condition improves under the influence of thiouracil. The average figure on discharge from hospital was 220 mgm. per cent. It would seem from this composite picture and from the reports in the literature that the blood cholesterol concentration should form a good index of progress and a reliable yardstick for the control of treatment. Unfortunately we have not found this to be the case; for though the average tendency works out well enough in a composite picture, yet in individual cases we have often found little correlation between the cholesterol reading and the progress of the case. The cholesterol concentration of one or two patients actually fell during treatment in spite of striking improvement in all other features. We do not believe, therefore, that this reading can be taken as a reliable means of controlling treatment from week to week.

The B.M.R.—With one exception all the cases have shown a significant fall in the B.M.R. reading under treatment. The final average reading before thiouracil was given was +44 per cent., and the final average reading before the patients left hospital was +8 per

cent. It will be seen that the latent period before a fall in the B.M.R. became noticeable averaged about ten days, and this fall reached significant proportions in about three weeks' time. There was only a very few days' variation from case to case in this respect. It was our custom to reduce the dose of thiouracil to a maintenance one as soon as the B.M.R. began to reach normal limits, and this could be done in from eighteen to twenty-six days, no matter whether the case was severe or mild.

The B.M.R. is a procedure which lacks universality of application in ordinary practice and is certainly not one which should be attempted on out-patients without admitting them to hospital for a night or more if accurate results are to be obtained. Even in hospital we find that

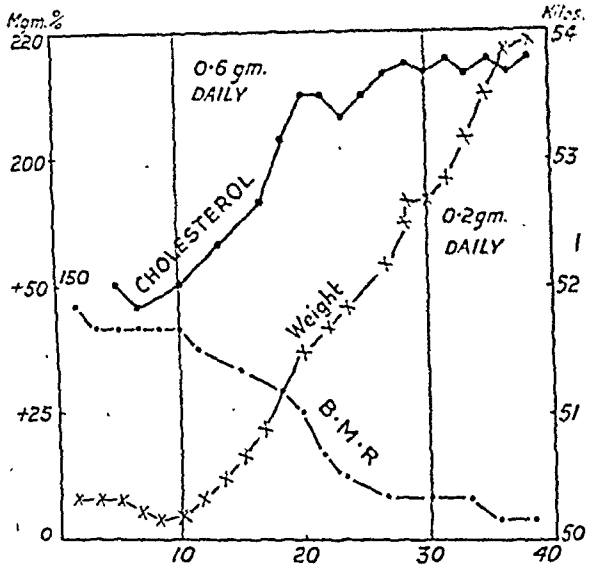


FIG. 2.—Composite picture of the effect of thiouracil in 31 cases of thyrotoxicosis on the blood cholesterol concentration, B.M.R. and weight.

many patients become over-anxious about their B.M.R. readings and in consequence artificially high estimations are obtained. The effect of thiouracil on the B.M.R., however, is on the whole so precise and invariable as to make B.M.R. readings superfluous in ordinary practice. The initial dosage may therefore be confidently reduced to a maintenance one in from three to four weeks' time.

The Weight.—With again one exception treatment has resulted in a substantial increase in weight. The gain in weight seemed to precede the fall in the B.M.R., but that may be due to the fact that the patients were weighed every day whereas the B.M.R. estimation was only made three times a week. The increase in weight might therefore on the average have been noted earlier than the fall in the B.M.R. The former usually became manifest about the eighth day of treatment. An average gain in weight of four kilos, or about nine pounds, was

registered during the month's treatment in hospital with thiouracil, but the weight almost invariably continued to rise after the patients left hospital, and several increases of well over two stones have been noted.

	Average B.M.R.	Average Weight in Kilos.
Before treatment . .	44 (68-33)	53 (60-48)
On discharge . . .	12 (17-9)	57 (67-52)
Final	7 (12-3)	60 (69-53)

The accompanying table shows the average effect of thiouracil on Professor Davidson's eight cases in hospital and while being subsequently observed as out-patients for periods varying from three to ten months. It will be seen that the results are very similar to my own.

The Pulse Rate.—As Himsworth [24] has pointed out, the drug does not act uniformly on all the signs of thyrotoxicosis. The first to show improvement is skin flush and the last tachycardia. Our experience has been similar. The pulse rate and blood pressure have not been included in the graphs shown as they would have unduly complicated them. Where a marked degree of tachycardia existed its control was delayed long after the B.M.R. had fallen nearly to normal and the weight and other symptoms had greatly improved. Where considerable tachycardia was present it often took a month or longer for thiouracil to control it; it would indeed be surprising if a heart which had been toxic for a long time recovered more rapidly. Patience, therefore, has sometimes to be exercised in this respect.

Auricular Fibrillation.—Three patients in my series suffered from auricular fibrillation. We know that after thyroidectomy a proportion of fibrillations—usually those of short duration—return spontaneously to normal rhythm. Many, however, continue to fibrillate and have to be restored to normal rhythm by the use of quinidine. This is indeed one of the chief indications for quinidine treatment. Rhythm was restored to normal by thiouracil in one of my three cases after a fortnight's treatment. Thiouracil was stopped after this result was obtained and a month later fibrillation recurred and was again abolished by thiouracil, since when normal rhythm has been maintained by maintenance dosage. A restoration to normal rhythm under thiouracil is recorded in four cases in the literature. My other two cases continued to fibrillate after a month's treatment, as did one of Professor Davidson's. In other respects they were steadily improving, though one showed slight residual signs of thyrotoxicosis after a month's treatment. Fibrillation was, however, made the excuse to carry out thyroidectomy, as we were anxious to see the effect of thiouracil treatment on the histology of the thyroid. In spite of a successful thyroidectomy fibrillation continued in all these cases, and normal rhythm was only restored

by the use of quinidine. There is no reason to believe that a similar result with quinidine and thiouracil would not have been obtained without resorting to thyroidectomy.

Glycosuria.—Glycosuria is found in many cases of thyrotoxicosis in association with a mildly diabetic blood sugar curve. Such cases may be cured of their diabetic tendency by thyroidectomy. There are, of course, other thyrotoxic cases with true severe diabetes, and this diabetes is not cured, though it may be ameliorated, by thyroidectomy. Two patients in my series had thyrotoxic diabetes with moderate diabetic sugar curves. They each had required for a long time insulin and careful dieting to control the glycosuria. In both cases thiouracil restored their sugar metabolism to normal so that they were able to dispense first with insulin and then with special dieting. These results are in accordance with the observations of other workers in this respect.

Exophthalmos.—The exophthalmos of the patients was not materially benefited by thiouracil. A slight improvement was noted in a few cases. It did not become worse in any of them. On the average this feature is definitely improved by thyroidectomy, though many cases are unaffected and very rarely the exophthalmos may become more marked after the operation.

Size of the Goitre.—On the whole, also, it has been found in my series and in the reports of others that thiouracil in the dosage used does not greatly influence the size of the goitre. Slight fluctuations in size have been noted from week to week and month to month. A fairly constant feature has been an increase in the size of the gland coincident with the menstrual period and a recession after it. Almost invariably the goitre has become softer in contrast to the firmer gland produced by iodine. With one exception, however, the changes in the size of the gland have not been material.

Theoretically it would seem that if the pituitary was stimulated to produce excess thyrotropic hormone by overdosage with thiouracil an increase in the size of the goitre would occur similar to the hyperplasia produced experimentally. This occurred in one patient who, owing to a misunderstanding, took 0·4 gm. daily—double the usual maintenance dose—for five and a half months. At the end of this time she was found to have developed a very large soft goitre and mild myxœdema.

Drug Resistance.—One patient in my series—an elderly woman with a nodular goitre—appeared to be drug resistant. In spite of a month's treatment the B.M.R. remained largely unaffected, the weight failed to rise and thyrotoxic signs persisted. Thyroidectomy resulted in improvement though some latent thyrotoxicosis persisted. I cannot account for this result which finds no real counterpart in the literature. It is true that Joll [24] reports three failures out of nine cases, chiefly on the grounds that tachycardia was unaffected. His results were criticised by Himsworth [24] as being founded on too short a period of observa-

tion, and it would indeed be surprising if one observer in such a small number of cases encountered such a high proportion of drug resistant patients. We may say then that if drug resistance does actually occur it must be excessively rare.

Toxic Effects.—The recorded signs of toxicity to thiouracil are fever, enlargement of lymph glands, rashes, swelling of the legs and feet, leucopenia, granulopenia, thrombopenia and acute sensitivity reactions. Of these the only serious signs calling for a cessation of treatment are the blood changes and acute signs of sensitivity. Slight swelling of the ankles and feet is the commonest manifestation. I have recorded it in three cases and Professor Davidson in two—that is in five out of thirty-nine cases—and this has been noted fairly frequently by other workers. The œdema is unassociated with cardiac failure or signs of renal damage and disappears though treatment is continued.

Only one of my cases developed serious toxic symptoms: A girl æt. 23 with a primary toxic goitre, a B.M.R. of +50 per cent. and a white count of 5100, was beginning to show a gratifying response to 0·6 gm. of thiouracil daily when on the twelfth day of treatment her white count dropped rather suddenly to 2000 and on the thirteenth day to 1900—the neutrophil differential count falling to 33 per cent. She felt well, but on account of the leucopenia and slight granulopenia the administration of thiouracil was stopped. In four days' time the white count had recovered to 4100 and the differential count to normal and the administration of thiouracil was resumed; but a quarter of an hour after the first dose of 0·6 gm. had been given a violent sensitivity reaction took place: there was severe headache and pain in the muscles, vomiting, swelling of the lips, face and ankles, a rise of temperature to 101°, tachycardia and a purpuric eruption in the bend of the elbow when the blood pressure was taken. The reaction took place at 6 p.m., the patient remaining ill during the night and recovering the next day. Recovery was complete in twenty-four hours. The platelet count remained normal during the reaction, but the white count fell to 1800, recovering in two days to 4100. A week later we gave her a single dose of 0·2 gm. thiouracil. The resulting histamine-like reaction, which occurred in a quarter of an hour and passed off in twenty-four hours, was identical to the first, save that no significant fall in the white count was noted on this occasion. The headache and pains in the muscles were intense, but were immediately relieved by an injection of adrenaline, which, however, had to be repeated on four occasions. Patch tests with thiouracil in hydrous eucerin made some days after the second reaction were negative. The patient was subsequently prepared for operation by the ordinary iodine technique and made a good recovery following thyroidectomy.

Out of the 135 cases reviewed in the literature, including Professor Davidson's and my own, 6 cases of leucopenia and granulopenia occurred, 1 fatal, 2 very slight, 2 severe with recovery and 1 reported by Newcombe and Deane [25] in which the leucopenia and granulopenia

were associated with thrombocytopenia and hæmorrhage. This latter case recovered, but is interesting as being the only case in which a serious reaction is reported after the dosage had been reduced to a maintenance one. All the others occurred during the earlier stages of treatment when the patient was receiving the larger initial dose. In Astwood's case the patient was receiving as much as 2 gm. of thiouracil a day at the time the agranulocytosis developed—a dose much larger than is now considered necessary.

The mortality from thiouracil treatment is thus lower than the mortality from thyroidectomy even in the hands of the best surgeons. Only one fatality has been reported, and we may take it that many more than the 135 cases reviewed here have been treated. Even if a

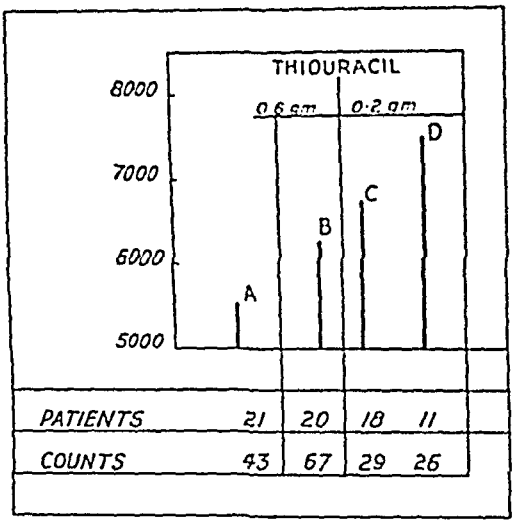


FIG. 3.—To show effect of thiouracil in dispelling the leucopenia of untreated thyrotoxicosis. (A) Average white count before treatment; (B) At end of initial treatment; (C) On discharge from hospital on maintenance dose; (D) On reporting as out-patients on maintenance dose.

very few other cases are made seriously ill by thiouracil we must remember that a considerable number of patients are made temporarily very ill by thyroidectomy. Further, it should be very rare for serious agranulocytosis to occur if frequent white counts are made during the initial treatment.

Contrary to expectation thiouracil treatment does not usually depress the white blood count, but rather the reverse. Untreated thyrotoxicosis is associated with a mild leucopenia, and as the thyrotoxic state is improved by thiouracil the count on the average rises significantly. (See Fig. 3.)

The capillary resistance tends to be generally low in untreated hyperthyroidism, and to show a tendency to rise as the condition improves under thiouracil. Certainly no significant fall occurred in any of the cases, save in the one which developed sensitivity. During

her reactions very low levels were observed, which may have been a factor in the production of the purpuric eruptions. It is unlikely, however, that a fall in the capillary resistance is the actual cause of the reaction, and such reactions cannot be predicted by observations on the capillary resistance.

Summary of Results.—In summary then, out of 39 cases observed by Professor Davidson and myself, 34 have been freed from their thyrotoxic symptoms by thiouracil treatment and have kept free and been able to return to their ordinary activities for periods of time varying from two to eleven months, though one of them has developed a goitre and temporary mild myxœdema through accidental overdosage. Three others have been operated upon on account of persistent fibrillation. Operation did not restore their fibrillation to normal rhythm, and quinidine was required. There is no reason to believe that quinidine would not have been equally successful in association with thiouracil. It might therefore be claimed that 37 of the cases were successful. One case appeared to be drug resistant and one other case required thyroidectomy because of the development of leucopenia and sensitivity to the drug. The reports in the literature are on the whole equally satisfactory. The results seem to be as good in severe cases as in mild, in secondary as in primary goitre, in old as in young.

Thiouracil prior to Thyroidectomy

From this study, therefore, it may be tentatively suggested that the results of thiouracil treatment are at least comparable with those of surgery. Even if this claim is not borne out by future experience it is possible that we have in thiouracil a drug which is in some respects superior to iodine in preparing a patient for thyroidectomy; for iodine seldom restores the metabolism of a severe case to normal, and, though it greatly improves thyrotoxic signs and symptoms, it only ameliortates them to a greater or less extent and does not hold them in complete abeyance as is usually the case with thiouracil. Further, there is a crucial moment to operate upon a patient who has been given iodine—between the seventh and the fourteenth day. If that moment is missed, owing perhaps to the patient or the surgeon developing a respiratory infection, it is necessary to wait for two or three months, and to start all over again, for it is highly dangerous to operate when the patient has become refractory to iodine and the B.M.R. is on the up-grade. With thiouracil the effect is permanent as long as the administration of the drug is continued, and any convenient date can be chosen for operation. There is, however, some evidence that the thyroids of patients prepared for operation by thiouracil are more vascular than those prepared by iodine, and this may constitute a drawback to thiouracil as a pre-operative drug.

The thyroids removed after pre-operative preparation by thiouracil are hyperplastic and largely free from colloid, showing in some areas

slight evidence of involution. The appearances do not differ materially from thyroids removed after iodine preparation. This is also the finding of other workers.

Ultimate Effects of Thiouracil

It remains to be seen what the ultimate effect will be of thiouracil treatment. It is clear at least that a maintenance dose must be continued for many months. In 2 cases we have discontinued the administration of the drug after treatment for two and three months respectively. In both cases a gradual return of thyrotoxic symptoms necessitated the resumption of treatment at the end of a month. Treatment has now been discontinued in 2 other cases who have been taking thiouracil respectively for nine and ten months. It is as yet too early to report the effect. Himsworth [21] reports 2 cases who have remained well after ceasing treatment for two and three months. There are theoretical grounds for believing that ultimate complete cure may result in at least a proportion of cases; for we know that long-continued hyperplasia may ultimately give way to atrophy of the thyroid, and if we can tide the patient over till this occurs the state of thyrotoxicosis may be cured.

Summary

These results suggest that we possess in thiouracil a drug with great potentialities. It can be given to all patients suffering from thyrotoxicosis with the virtual certainty that after a short latent period improvement will occur. The initial dose should not be larger than 0·6 gm. daily, and this should be administered for at least three weeks, and not longer than four weeks, when a maintenance dose should be given. During this initial period a white blood count should be made three times a week. If the count falls below 3000 the drug should be stopped, and if necessary the patient can be prepared for thyroidectomy with iodine. The maintenance dose should not be more than 0·2 gm. daily—probably 0·1 gm. is sufficient. There is little danger of serious toxic reaction or overdosage on the maintenance dose. It is not yet possible to speak dogmatically of the more remote prospects of eventually being able to stop the administration of the drug without fear of a return of thyrotoxic signs and symptoms.

I am greatly indebted to Dr J. B. Donald for much clinical assistance, to Miss E. Gilchrist for numerous estimations of the B.M.R., to Dr H. Scarborough for observations on the capillary resistance, and to Mr J. M. Graham for his surgical collaboration and for supplying me with the histological specimens of thyroids removed after pre-operative preparation with thiouracil.

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NOTE

Royal College of Surgeons of Edinburgh

AT a meeting of the Royal College of Surgeons of Edinburgh, held on 19th December, Professor R. W. Johnstone, President, in the Chair, the following who passed the requisite examinations were admitted Fellows:—Robert Smillie Barclay, M.B., CH.B., UNIV. GLASG. 1935, M.D. 1941; Marjorie Ruth Elizabeth Boyd, M.B., CH.B., B.A.O. UNIV. DUBLIN 1933, M.D. 1939; Robert Benjamin Wellesley Cole, M.B., B.S. UNIV. DURHAM 1934; Leonard Goodman, M.R.C.S. ENG., L.R.C.P. LOND. 1938; Samuel William Gilbert Hargrove, M.B., B.CH. UNIV. CAMB. 1937; Leslie William Hefferman, M.R.C.S. ENG., L.R.C.P. LOND. 1920; Mary Kathleen Lawlor, M.R.C.S. ENG., L.R.C.P. LOND. 1924; Francis Joseph Lorriman, M.B., B.S. UNIV. DURHAM 1924, M.D. 1939; Gardiner Mitchell, M.B., CH.B. UNIV. BIRMINGHAM 1937; Douglas Robert Kay Reid, M.B., CH.B. UNIV. ST ANDREWS 1942; Paul Steinar, M.R.C.S. ENG., L.R.C.P. LOND. 1942.

Higher Dental Diplomates.—The following candidates, having passed the requisite examinations, were admitted Higher Dental Diplomates:—Elwyn Lloyd Hampson, B.D.S. UNIV. LIVERPOOL 1939; Frederick Ian Robertson, L.D.S., R.C.S. ENG. 1930; Olive Edward Sharland, L.D.S., R.C.S. ENG. 1938.

NEW BOOKS

Chemotherapy of Gonococcic Infections. By RUSSELL D. HERROLD. Pp. 137. London: Henry Kimpton. 1943. Price 15s. net.

In this monograph Professor Herrold analyses the results of chemotherapy in approximately 1800 cases treated with various sulphonamide derivatives, sulphathiazole being the drug used in the majority. In an introductory chapter there occurs this illuminating sentence which arouses visions of the White Paper by the assertion: "It is obvious that many physicians have insufficient time or facilities to make microscopic studies in the diagnosis and determination of cure." The author endeavours to remedy these defects by allotting two chapters to diagnosis and one to determination of cure. Special attention is also devoted to "The Management of Sulfonamide Failures," and this valuable contribution to the literature is completed by the inclusion of chapters on "Infections in Women," "Infections in Children," and "Epidemiology." The last quarter of the text is given to recounting "Illustrative Case Histories." Altogether a forward-looking and forthright presentation of a subject of immediate and increasing importance.

Vascular Responses in the Extremities of Man in Health and Disease. By DAVID I. ABRAMSON, M.D., F.A.C.P. Pp. x+412, with 59 figures. Chicago, Illinois: University of Chicago Press. 1944.

The author is in charge of cardiovascular research in a hospital in Cincinnati, and conceived the idea of putting his knowledge of the literature on vascular responses in the extremities at the disposal of the medical profession. The debt which other workers in this field now owe him may be measured by the size of the present volume, which analyses the most important papers on the subject with great clarity and without verbosity, and includes at appropriate places the author's personal comments

on the reliability of techniques and the value of various forms of treatment. The book follows a well-designed plan. After a short section on the anatomy and physiology of the peripheral blood vessels, there are considered in turn methods of studying blood-flow in them, their physiological responses, their pharmacological responses, their blood-flow in abnormal states, in systemic disease, and in peripheral vascular disease, and finally their response when diseased to various forms of treatment. The monograph is a valuable source of information, providing not only basic facts but also, through the references at the end of each chapter, rapid access to particular aspects of the subject.

Doctor in the Making. By A. W. HAM, M.B., and M. D. SALTER, M.A., PH.D. Pp. 120. London: Medical Publications Ltd. 1944. Price 9s. 6d. net.

The total amount of information placed before the medical student of to-day is truly appalling, and it is difficult even for well-prepared individuals to cope with the course unless they are efficient students.

Some years ago in Toronto University a committee was set up to investigate those medical students whose performance in their first year was not in accord with what had been predicted for them from their past scholastic records. The committee soon discovered various factors which determined whether a student could achieve the success predicted for him. Later the committee turned its attention to advising the students, and the experience so gained forms the basis of this book.

The advice given in this helpful book should be considered by the teachers as well as by the students for whom it is primarily intended.

Regional Analgesia. By H. W. L. MOLESWORTH. Pp. viii+90, with 42 illustrations. London: H. K. Lewis & Co. Ltd. 1944. Price 8s. 6d. net.

This small book is an account of the author's personal experience of some 1500 operations carried out under regional analgesia, 500 of them of major severity. The indications for this form of anæsthesia are interesting, and apart from those cases whose hold on life is so weak and on whom a local anæsthetic is the only choice, the author employs regional anæsthesia in a group because the proposed operation is rendered easier and safer, and he includes in this group operations on the stomach, neck, hands or feet, difficult hernias and severe operations on the perineum and perineal repair in the aged.

The general principles of the method and its application to the various regions of the body are fully described and the monograph concludes with a chapter on spinal anæsthesia. Excellent descriptions are given of the analgesia of such important areas as fingers and toes, and of brachial plexus block and caudal block. For spinal anæsthesia the dry powder of Novocaine 0·1 gm. is used in a glass ampoule and dissolved in the patient's own cerebro-spinal fluid. This is re-injected into the subarachnoid space with gentle barbotage. This is certainly the method of choice and it seems surprising that so many complications are enumerated.

Altogether this is a most useful book. It is well written and illustrated and should be in every young surgeon's library.

Endocrine Man. A study in the surgery of sex. By L. R. BROSTER, O.B.E., D.M., M.CH. Pp. xi+144. London: William Heinemann (Medical Books) Ltd. 1944. Price 12s. 6d. net.

The title of this book is somewhat misleading, for it has little to do with surgery. The author sets out to stress the important part played by hormones of the endocrine glands in the automatic regulation of the body. A good deal of attention is given to a study of the functions of the suprarenal cortex. The book covers a very wide range of subjects from zoology and simple physiology to the intricacies of psychology. Its purpose is not altogether clear, but it contains a vast amount of interesting material.

NEW EDITIONS

Textbook of Surgical Treatment. Edited by C. F. W. ILLINGWORTH, M.D., CH.M., F.R.C.S.E., aided by 18 contributors. Second Edition. Edinburgh: E. & S. Livingstone Ltd. 1944. Price 30s. net.

The rapid appearance of a second edition of this work indicates clearly its merit and its popularity.

The book makes an approach to the subject rather different from the usual manual of operative surgery. It covers a wider field, including all forms of surgical care. Meticulous attention to details of operative technique are of less importance to the student and the post-graduate than a knowledge of surgical treatment in the wider sense. The writers devoted special attention to the choice of methods, to indications for and against operation and to the dangers and complications which may arise.

This thoroughly practical book is assured of continued success.

Pye's Surgical Handicraft. Edited by HAMILTON BAILEY, F.R.C.S. Fourteenth Edition. Pp. x+628, with 724 illustrations. Bristol: John Wright & Sons Ltd. 1944. Price 25s. net.

Pye's Surgical Handicraft needs no introduction for it has been a trusted standby since 1884. With the assistance of a large team of contributors Mr Bailey has recast the matter to harmonise with current practice. In these strenuous days leisurely reading is out of the question, so the editor has planned to save the reader's time in building up a conception of the written word by a very liberal use of illustrations.

This excellent book may be regarded as the house surgeon's *vade mecum*.

Treatment by Manipulation. By A. G. TIMBRELL FISHER. Fourth Edition. Pp. viii+224, with 81 illustrations. London: H. K. Lewis & Co. Ltd. 1944. Price 16s. net.

Since the last edition of this well-known and popular textbook many additions and alterations have been made, including the re-writing of several sections.

It is a timely appearance since the subject of manipulation has assumed even greater importance during the war, not only in the saving of valuable time in the treatment of injuries when man-power is so vital, but in the later stages of treatment of the disabilities that are the aftermath of war.

The book starts with a most interesting historical introduction, giving the reader some idea of the attitude to manipulative surgery of such men as John Hunter, Hilton, and H. O. Thomas.

The two main aspects of the subject—diagnosis and treatment—are very fully described, and it is emphasised how necessary the first of these is in avoiding some of the disasters that often accrue from treatment by bone-setters and such unqualified practitioners. Low back pain is described very fully and the differential diagnosis of its various causes, including particularly lumbo-sacral and sacro-iliac pain, reviewed so clearly and concisely that it almost sounds easy.

The chapter on The Cult of Osteopathy should be reprinted and widely circulated. Although the orthopædic surgeon in the manipulative branch of his speciality is thought by many to be doing little more than the osteopath, the essential difference is emphasised in this book. The author points out that the orthopædic surgeon may manipulate the spine for the release of adhesions there, but the osteopath does it, not because the spine is itself the seat of symptoms, but in misguided attempts to cure some disease—for example, epilepsy, diabetes, or even cancer.

This is a splendid book which every orthopædist has in his library and which should certainly be in the library of many other practitioners.

Fractures and Fracture Treatment in Practice. By K. COLSEN. Second Edition. Pp. 156, with 163 illustrations. Johannesburg: Witwatersrand University Press. 1944. Price 12s. 6d.

In this small book the author has attempted, very successfully, to give to students and practitioners a brief review on broad lines of the subject of fracture treatment. He has had in mind particularly the qualifying examination for the former class of reader.

The first nine chapters of the book are concerned with more general considerations —the causes, healing, treatment and complications—while the second part is devoted to the individual fractures. There is little to criticise in the material provided, and the author appears to have been guided by Böhler and Watson-Jones in the treatment of compound fractures.

It is interesting that the author still advises the ether-iodine method, does not flush out the wound, and attempts at all costs, even to the use of tension incisions, to suture the wound.

The diagrams, though crudely done, are fully explanatory and the letterpress, while brief and concise, is adequate for its purpose.

Materia Medica. Pharmacy, Pharmacology and Therapeutics. By WILLIAM HALE WHITE, K.B.E., M.D. (LOND.), M.D. (DUBLIN), LL.D. (EDIN.). Twenty-sixth Edition. Revised by A. H. DOUTHWAITE, M.D., F.R.C.P. Pp. 534.. London: J. & A. Churchill. 1944. Price 14s.

This book retains the characteristics of previous editions, though, on account of the introduction of several new potent therapeutic agents within the past two years, it is rather longer. The latest information on these advances is included in this edition, which is assured of the popularity enjoyed by previous ones, for it is a compact book containing an adequate description of all the useful drugs in present use.

A Synopsis of Hygiene (Jamieson and Parkinson). By G. S. PARKINSON, with a Section on Personal Hygiene by G. P. CROWDEN. Eighth Edition. Pp. xvi+ 719, with 16 illustrations. London: J. & A. Churchill Ltd. 1944. Price 25s. net.

The ground covered by this volume is very extensive, and includes all branches of public health practice in the widest sense. It is full of information.

In this edition there is a summary of the proposals for a National Health Service in addition to new material in sections on chemotherapy, on certain diseases such as infectious jaundice, and on parasitology, with revisions in other sections.

There is only one criticism: Scottish public health law is not included.

The book is written in a very lucid and pleasant style, and a valuable feature is the inclusion in the text of references to numerous papers on the subjects dealt with.

This is a thoroughly good book.

BOOKS RECEIVED

Edited by BELL, E. T., M.D. A Text-book of Pathology. Fifth Edition.	(*Henry Kimpton, London*)	45s. net.
MEAKINS, JONATHAN CAMPBELL, M.D., LL.D. The Practice of Medicine. Fourth Edition	(*Henry Kimpton, London*)	50s. net.
SEVAG, M. G., PH.D. Immuno-Catalysis. (*Charles C. Thomas.*)	(*Distributors in the British Isles, Baillière, Tindall & Cox, London*)	$4.50 Post paid.
SHAW, WILFRED, M.A., M.D., F.R.C.S., F.R.C.O.G. Textbook of Gynæcology. Fourth Edition	(*J. & A. Churchill Ltd., London*)	24s. net.
ZOETHOUT, WILLIAM D., PH.D., and W. W. TUTTLE, PH.D. Textbook of Physiology. Eighth Edition . . .	(*Henry Kimpton, London*)	25s. net.

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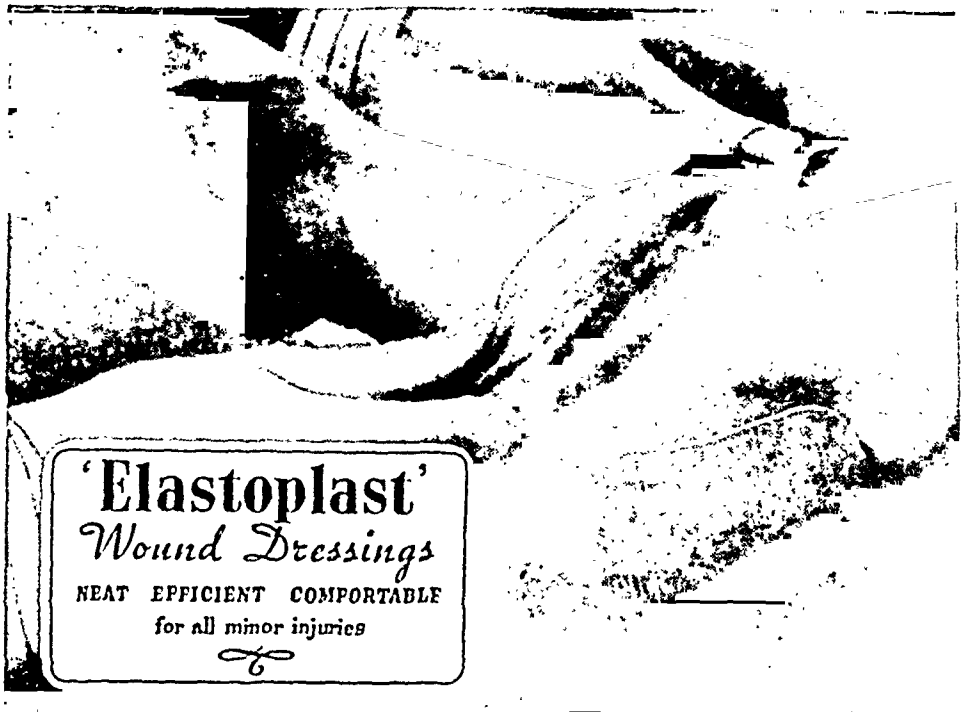

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Edinburgh Medical Journal

February 1945

MENINGOCOCCAL ENDOCARDITIS: A REVIEW

By W. R. LOGAN, M.D., F.R.C.P.Ed., D.P.H.

Bacteriologist to the Royal Infirmary, Edinburgh

Historical.—The first case of meningococcal endocarditis to be recognised was that of Warfield and Walker (1903). He was a negro of 32 years, an alcoholic who had been on a drinking bout. He was delirious when admitted to hospital on 23rd March, and no history could be obtained from him. His illness dated from about a week before admission, but his relatives said that he had had a previous similar attack about a year before. He had a remittent pyrexia. In his delirium he jumped out of a second-storey window in the hospital, breaking a bone in the right ankle. His heart's action was irregular, he had a rough systolic murmur at the apex transmitted into the axilla and the second aortic and pulmonic sounds were accentuated. Blood culture taken on 12th April yielded a meningococcus. There was no clinical evidence of meningitis. He died on 22nd April. Post-mortem examination showed a marked chronic endocarditis of the mitral valve with stenosis, and, on top of this, extensive pale grey and red fungating vegetations, the largest mass projecting 3 cm. into the cavity of the heart. The aortic valves were uniformly thickened and slightly retracted, with a pin-head sized fresh vegetation on each leaflet. The heart muscle was soft and friable, there were infarcts in the spleen and kidneys, and chronic diffuse and glomerular nephritis. Meningococci were cultivated from the vegetations. The brain was not examined, and meningitis was thus not absolutely excluded. There were no details available as to his previous attack of endocarditis, which presumably took place during the delirious fever of the previous year.

Claude and Bloch (1903) described a case in which death took place from meningitis, and post-mortem examination showed recent endocarditis, but it was doubtful whether the organism obtained was a meningococcus. Results with Gram's stain were variable, its viability on artificial media was longer than that of the meningococcus, and it sometimes grew in short chains. It is possible they were dealing with a mixture of meningococci and streptococci.

In 1905 Weichselbaum and Ghon described a case of fatal meningococcal meningitis in which early endocarditis of the mitral valve was found at post-mortem examination; meningococci were grown from the vegetation. Schottmüller (1905) briefly described a case in which meningococci were obtained from the vegetations of ulcerative endocarditis, and there was definitely no meningitis. Westenhoeffer (1906) described two cases occurring

after primary meningococcal meningitis, but did not prove that the endocarditis was meningococcal. The second American case was reported by Cecil and Soper (1911). The patient had a history of two attacks of rheumatism, and the diagnosis was rheumatic fever and endocarditis till meningococci were obtained from the blood. Post-mortem examination showed both old and recent endocarditis, and fibrous adhesions of the pericardium. Meningococci were obtained from the vegetations. There was no meningitis.

Since then, rare cases have been reported, in some of which endocarditis was found post-mortem after death from meningitis, while in others it sometimes occurred without or preceding meningitis. In addition, there are cases of meningococcal infection in which there was a varying degree of clinical evidence of endocarditis.

The Cases Analysed.—There have been collected for analysis 31 cases of meningococcal endocarditis, proved either by death and post-mortem examination, or by such evidence as cardiac insufficiency or infarctions. In addition, there are 25 cases of meningococcal infection, all showing cardiac murmurs, in which there was a varying degree of evidence of endocarditis. These 25 cases were divided, as will be explained, into three groups: "probable," "possible," and "unlikely, or proved negative" cases.

Twenty-nine of the 31 proved cases were fatal, either from meningitis or endocarditis, and in 27 post-mortem examination was carried out and vegetations found. In two fatal cases, Zeissler and Riedel's (1917) first case and Heinle's (1939) fourth (meningococcæmic) case, there was no post-mortem examination. Two cases, those of Zeissler and Riedel (second case) and of Cutts, Krafft and Willcox (1942), recovered. In these 4 the evidence, including that of valvular insufficiency, sometimes of infarctions, was such that there could be no doubt as to the diagnosis.

Fourteen were primarily cases of cerebrospinal meningitis; in 4 of these death took place from endocarditis after recovery from meningitis. In 17 there was infection of the endocardium without primary meningitis; in 3 or perhaps 4 of these meningitis developed later.

There are thus 31 cases of proved endocarditis in the series and, if we accept the "probable" group, other 10 cases, or about 41 in all. A few other cases have been reported, but the records of these were unobtainable.

Reference to the cases in each category will be found in the bibliography.

The Nature of the Lesion.—Cases of meningococcal endocarditis occurring in the course of fatal primary meningococcal meningitis give us some very early endocardial lesions, of which the maximum possible age can be determined. In Krumbhaar and Cloud's (1918) second case, a young soldier, death occurred within 72 hours of the beginning of illness. Post-mortem examination showed near the base of the mitral leaflets numerous minute glistening vegetations which could easily be wiped off. Smears from these showed numerous polymorphonuclear and endothelial cells and many Gram-negative diplococci.

Their third case, also a young soldier, died after 4 days' illness with meningitis. Necropsy showed a pale and flabby heart with some dilatation of the right chamber. There were a few pinpoint glistening spots on the mitral valve shown by smears to contain leucocytes and a moderate number of Gram-negative diplococci.

In Westenhoeffer's (1906) second case, a young woman, also with meningitis,

death took place after 5 days' illness and both mitral leaflets were found to be seats of fresh grey vegetations. This paper was not obtainable in the original, and more exact details are not available.

As far as can be ascertained there was no clinical evidence of endocarditis in any of these early cases.

When the illness was of longer duration it became more difficult to estimate the propable age of the endocardial lesion. Death took place on the 19th day in Krumbhaar and Cloud's (1918) first case, a soldier of 28 years. On the posterior aortic valve there was a rather soft, flat, greyish vegetation 3 mm. in diameter, while on the anterior aortic and both mitral valves there were several soft, glistening, yellowish minute spots which were easily wiped off. In Westenhoeffer's (1906) first case the duration of illness was 3 weeks; on one of the mitral leaflets there were small greyish vegetations the size of peas. Weichselbaum and Ghon's (1905) case, a 9-weeks' old child, died after an illness of 5 weeks, and a vegetation on the mitral valve was the size of a small strawberry.

When we study the cases of meningococcal endocarditis without primary meningitis, it becomes even more difficult to determine the date of onset even approximately. In Melnotte and Fort's (1932) case, for example, the patient, a young soldier, was admitted to hospital with a diagnosis of gastric ulcer. It was found clinically that he had an aortic lesion. Within 3 weeks he was dead, and post-mortem examination showed enormous ulcero-vegetative lesions of the aortic valve. There was no gastric ulcer. It was impossible to estimate the duration of the endocarditis.

Descriptions of the affected valves were available in 23 cases, including both meningitic and ameningitic varieties. Some of these are: "cauliflower vegetations the size of a hazel-nut" (Ribierre, Hébert and Bloch, 1919); "large vegetations on the mitral valve about the size of the terminal phalanx of the thumb almost completely occluding the orifice (Wright Mackarell, 1915); "ulcerative endocarditis" (Warfield and Walker, 1903, and others); "three pea-sized masses attached to free margins of aortic valve: bright red, each with a small pedicle. Very friable" (Hyland, 1929); "soft white friable vegetations of considerable size" (Stevenson, 1931); "vegetations on mitral valve, valve leaflets partly necrotic" (Willius and Eaton, 1937); "the two posterior flaps of the aortic valve showed deep ulceration with vegetations" (Denehy, second case, 1926); and so on.

It was evident in a few cases that vegetations present were of differing age, and in 4 there was recent endocarditis super-imposed on an old healed lesion: Warfield and Walker (1903), Cecil and Soper (1911), Gwyn (1931) and Lemierre, Laporte, Reilly and Laplane (1934). In the first three it was probable that the old endocarditis was due to a previous infection by another organism and was perhaps rheumatic in nature. Gwyn believed it to be an old rheumatic lesion in his case. In the last both old and recent lesions were almost certainly due to the same meningococcus infection.

The *valves affected* in these 23 cases were: the mitral alone thirteen times; the aortic alone seven times; the mitral and aortic twice; and the tricuspid, affecting by extension the aortic (Rhoads, 1927), once.

As might be expected from the friable nature of the vegetations *infarcts* of the spleen or kidney or both were common, being present in more than half of the cases. There was cerebral embolism in 2 cases reported by Denehy (1916), and in the cases of Lemierre, Laporte, Reilly and Laplane (1934) and

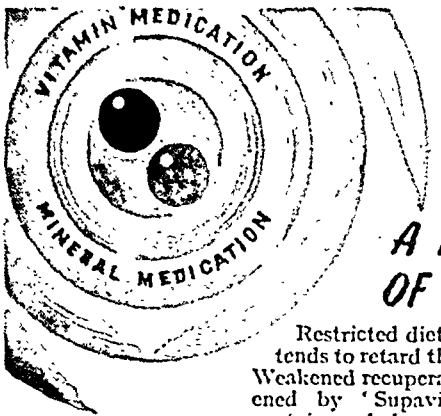
Willius and Eaton (1937). There was clinical evidence of pulmonary infarction in Zeissler and Riedel's (1917) second case, and in Heinle's (1939), and Cutts, Krafft and Willcox's (1942) cases.

It is evident that a few of these cases of meningococcal endocarditis resembled the acute bacterial endocarditis due to the hæmolytic streptococcus or the gonococcus, while most were more like the subacute bacterial type due to streptococcus viridans. But we are in the difficulty that these cases were selected as definite and proved cases of meningococcal endocarditis because they were fatal and proved by post-mortem examination, or because infarctions were produced, and we are still left with the question as to whether milder types of endocarditis occur, from which the patient makes a complete recovery.

The Development of Endocarditis during or after Primary Meningitis. —What is required to answer this question is the death of cases of endocarditis from a cause other than the endocarditis, with subsequent post-mortem examination. Meningitis might have been expected to give help in this matter; but an analysis of the 14 cases of endocarditis arising after primary meningitis gives no definite answer. In the cases in which death occurred early the endocardial lesions were in an early stage, and how they would have developed had the patient not died was a matter of speculation. On the other hand, where the illness was prolonged death occurred from endocarditis and not from meningitis, so again we were dealing with fatal endocarditis.

A description of three of these will show how the development of the condition may vary. Weindel's (1934) case, a woman, made an apparent recovery from meningococcal meningitis under serum therapy. After 26 days from the onset, the cerebrospinal fluid being clear and the temperature normal, she was allowed up, but it was noted that she had a slight systolic murmur. On the 46th day she was allowed home. Three weeks after discharge and 9 weeks from the beginning of the illness, she returned. She had had altogether a fever-free period of 6 weeks, but at the end of that time had begun to have shortness of breath, and finally pain in the heart region, vomiting and high fever. Signs and symptoms of insufficiency developed, blood cultures were repeatedly positive, and she died about 11 weeks after the beginning of the illness. Post-mortem examination showed ulcerative endocarditis of the mitral valve, widespread toxic changes, bronchopneumonia, œdema of the lungs, and infarcts in the spleen and one kidney.

The second case, reported by Lemierre, Laporte, Reilly and Laplane (1934), was a farmer, aged 52. His meningitis yielded to serum treatment in about a month and a half, with apparently definite recovery, but there was a recurrence two months later. There was again recovery in about 15 days following two intrathecal injections of meningococcus endoprotein. Seventeen months of good health followed, during which he worked as a farmer. He then had an apoplectic stroke with left-sided hemiplegia. He was found to have a double aortic murmur, and blood culture yielded meningococcus Type B (Group II). Death took place 18 days after the stroke. At post-mortem examination a large vegetation was found implanted on an aortic cusp, which was fibrous and had been organised a long time previously. One of the neighbouring cusps bore smaller vegetations. There were recent embolic lesions in the right cerebral hemisphere, the spleen, and the kidneys. The authors believed that the endocardial lesion dated from the beginning of the illness and had accordingly existed for 21 months without clinical manifestation.



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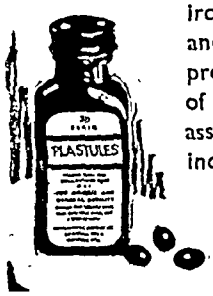

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In a third case, that of Stevenson (1931), the patient died after 4 months' illness. At post-mortem she was found to have chronic meningitis as well as endocarditis of the mitral valve, but it was not possible to determine the date of infection of either meninges or endocardium. She had been in hospital, had left at her own wish, and had been readmitted 6 weeks later. This patient was the one described elsewhere as saturated with meningococci at the time of death.

Clinical Analysis of Cases of Meningococcal Endocarditis without Primary Meningitis.—This analysis was made chiefly to determine in what ways these proved cases of endocarditis differed clinically from ordinary cases of meningococcæmia, so that some guidance might be obtained in judging whether the other suspected cases were or were not cases of endocarditis. It is with the earlier stages that we are mainly concerned. In the later stages, with the appearance of the effects of valvular insufficiency, sometimes with the occurrence of infarctions, the diagnosis could no longer be in doubt.

It was found that clinical details were insufficient in 5, so 12 cases were available for analysis. These were the cases of Warfield and Walker (1903), Cecil and Soper (1911), the two of Zeissler and Riedel (1917), and those of Ribierre, Hébert and Bloch (1919), Hyland (1929), Gwyn (1931), Stevenson (1931), Melnotte and Fort (1932), Willius and Eaton (1937), Heinle, fourth case (1939), and Cutts, Krafft and Willcox (1942). Nine of these cases were fatal.

There was obviously a much greater chance of endocarditis being diagnosed during life in these cases than in the meningitic group, which were usually of shorter duration, and in which the meningitic symptoms overshadowed all others. Murmurs in the mitral or aortic areas, or both, were present in all cases.

Taking as the diagnostic features of pure meningococcæmia intermittent fever, skin lesions coming out in crops with the rises of temperature, and pain in joints with or without swelling, Zeissler and Riedel's first case, and Gwyn's case, both fatal, were the two conforming most nearly in the earlier stages to the clinical picture of meningococcæmia. It seems from the description of the other cases that the condition was usually suggestive, from an early stage, of endocarditis rather than of meningococcæmia. That is, it was only the finding of the meningococcus in the blood stream that differentiated the condition from a subacute bacterial endocarditis due to streptococcus viridans. None of the cases showed the malaria-like periodicity of pyrexia, except that the daily intermittent type was sometimes observed. The recurrent skin lesions of the erythema nodosum type were hardly ever seen; petechial eruptions were frequent, especially in the later stages, as they are in a streptococcal endocarditis. Heavy sweats were mentioned in 4 of the 11 cases, and these in a case of meningococcæmia might arouse suspicion of endocarditis, because although sweating is common in meningococcæmia after a pyrexial period, it is not usually of this drenching character. The other features which an analysis of these cases suggest as indicative of endocardial involvement, apart from the results of valvular insufficiency, were increasing "illness" of a patient with loss of weight and sometimes anæmia, while evidence of infarction was to be found in pain in the chest with bloody sputum, the passing of blood in the urine, or pain over the splenic area. Cerebral embolism did not occur in any of these cases.

As regard the nature of the *heart murmurs*, the following are some of the descriptions along with clinical or post-mortem evidence: pre-systolic and systolic at apex (*post-mortem old mitral stenosis, recent mitral and aortic* endocarditis); soft systolic at apex (no post-mortem); systolic and diastolic, later diastolic only at base (aortic insufficiency clinically); diastolic heard best at aortic area (aortic vegetations post-mortem); loud systolic in mitral area, diastolic in aortic (post-mortem, old and recent mitral endocarditis, aortic valve clear); systolic and diastolic all over precordial region (aortic insufficiency clinically and post-mortem); loud blowing systolic murmur best heard at apex, but also in axilla, *pulmonic second sound accentuated* (post-mortem mitral endocarditis); harsh systolic murmur at apex (no post-mortem); rough diastolic in aortic area, soft systolic at apex (clinically aortic insufficiency with recovery).

Among clinical features which gave no help in the differential diagnosis, rigors were mentioned in 3 cases only, being specially marked in Heinle's cases. There was arthralgia in 2 of the 11 cases, arthritis in other 2. Enlargement of the spleen, rather surprisingly, was on the average detected less commonly in these cases than in pure meningococcæmia. Clubbing of fingers was not mentioned in any of the cases.

Appelbaum (1937) claimed that a progressive rise of *bacterial colonies in blood cultures* is corroborative evidence of endocardial infection, but unfortunately observations in definite cases of meningococcal endocarditis are scanty. As will be described in a later paper, there is evidence that colony counts are higher in endocarditis than in pure meningococcæmia.

A definite impression was obtained from the examination of these records of proved cases that they were not usually cases of meningococcæmia in the course of which there was a development of endocarditis. They were cases of primary meningococcal endocarditis, and from the beginning of the illness they resembled subacute bacterial endocarditis, or occasionally rheumatic endocarditis rather than meningococcæmia. The presumption is that the meningococcus only primarily attacks valves which are susceptible for some rarely occurring reason. The fact that 3 cases showed an old healed endocarditis suggests that meningococcal endocarditis might occur only if there had been a previous fault in the valve such as a rheumatic lesion. It must be admitted that only 1 of the 11 cases had a rheumatic history, but in several there is no mention of enquiry as to previous rheumatism.

The *duration of the endocardial condition* in cases in which death was due to endocarditis was not easy to establish. The duration of illness was stated to be 17 days in a case described by Rhoads (1927). The patient was a young negro. Post-mortem examination showed vegetations and ulcerative endocarditis of the tricuspid valve with perforation through the interventricular system, and affecting the aortic valve. The maximum duration is determinable with more certainty in Weindel's (1934) case, where death took place from endocarditis after definite recovery from meningitis; the maximum possible duration was 11 weeks. The cases of longest duration were probably Gwyn's, and Willius and Eaton's, of upwards of 8 months and 9½ months respectively, while Cutts, Krafft and Willcox's case recovered after over 9 months' illness.

Treatment.—Six of these 11 cases were treated with antimeningococcal serum, one of them with some sulphanilamide in addition, but all died. Two were influenced unfavourably by the serum, one (that of Ribierre, Hébert and Bloch) dying from anaphylactic shock, while in Stevenson's case there

was ecchymosis after its use as if it might have caused a liberation of toxins. These figures are a little unfair in an evaluation of the efficacy of serum treatment, as we are dealing here largely with those cases of endocarditis proved by post-mortem examination. One patient, reported by Cutts, Krafft and Willcox (1942), was given intense sulphonamide therapy over a period of 9 months, and recovered completely. He received 90 gm. of sulphanilamide, 130 gm. of sulphapyridine, and 560 gm. of sulphathiazole. He was very ill, and was undoubtedly saved by the treatment.

Types of Meningococci in Endocarditis.—The meningococcus was obtained by blood culture, or by film or culture from the vegetations, or from both sources in 29 of the total 31 cases of endocarditis, including those with primary meningitis. In two it was obtained only from the cerebrospinal fluid.

The type of meningococcus was proved in 11 cases. These yielded one Type 1, two Group I (one being the French Type A), two Type 2, three Group II (one being the French Type B, another a parameningococcus), one "irregular" parameningococcus, one "agglutinated with standard sera" (probably Group I or II), and one agglutinated by all 4 sera. That is, 3 definitely Group I, 5 definitely Group II, and 3 others.

As the number of Group I blood infections is greater than that of Group II, the proportion of Group I meningococcæmias to those due to Group II being a little over 4 : 3 (later paper), while the blood infections in epidemics of meningitis are obviously much more commonly due to Group I than to Group II, it is evident that Group II meningococcus has a greater tendency to cause endocarditis than has Group I meningococcus.

If we compare the *mortality* in Group I and II cases in which death was due to endocarditis, directly or indirectly, and not to meningitis, anaphylaxis or other complications, and eliminating the Group II case of Cutts, Krafft and Willcox saved from almost certain death by intensive sulphonamide therapy, we find that the 3 Group I cases and the 3 Group II cases were all fatal. A fourth Group II case died of anaphylaxis. These figures are in contradiction of Branham's statement (*Bact. Rev.*, 1940, 4, 59) that ". . . there are few fatal cases of endocarditis due to Group II meningococcus; fatal meningococcus endocarditis is usually found to be due to Group I strains." Further, as will be shown in a later section, there is no evidence that cases of endocarditis which recover are usually due to Group II; in 7 of the 10 "probable" cases there was recovery, but the meningococci in 6 of the cases were not typed, and the organism in the 7th case was Group I.

Cases of Probable or Possible Endocarditis.—This series consists of an additional 25 cases of meningococcal infection showing heart murmurs but in which the diagnosis of endocarditis, if made, was based on clinical grounds only, and in which such evidence as the occurrence of infarction was lacking. Six of the cases were fatal, but there was late meningitis in three of these, and chronic nephritis in a fourth.

The 25 cases were first divided into three groups: the first contained those cases in which a definite diagnosis of endocarditis was made by the physician on clinical grounds; the second those cases in which this diagnosis was considered, but not finally held as certain on clinical grounds; the third group those cases in which the presence of cardiac murmurs did not in the view of the physician justify this diagnosis. The classification is somewhat arbitrary, as it is clear that some physicians made the diagnosis on rather slender grounds, while others took a conservative view when the evidence was

much more complete. Fifteen cases fell into the first group, 5 into the second, and 5 into the third group.

On analysis, 5 cases were eliminated from the first group of "probable" cases. The evidence was insufficient in the cases of Landry and Hamley (1919), and Krusen and Elkins (1937). Three other cases were excluded by negative post-mortem evidence: Dock's (1924) case, Kennedy's first case (1926), and Harrison and Abernethy's first case (1934). Kennedy's patient was in many hands during his long illness of two years and four months, and the diagnosis was made by several physicians; others, however, considered the murmurs to be functional. There were no vegetations to be found in these 3 cases.

Ten cases therefore remained in the "probable" group: those of (1) Marfar and Debré (1910); (2) Bittorf (1915); (3) Hennell and Wiener (1930); (4, 5, 6) Master (1931); (7, 8, 9) Appelbaum (1937); and (10) Heinle, fifth case (1939).

The "possible" group now contained 7 cases: those of Landry and Hamley, and of Krusen and Elkins, relegated from the first group, along with those of Bray (1915), Kennedy, third case (1926), Harrison and Abernethy, second case (1934), Stewart-Wallace (1936) and Appelbaum's (1937) "doubtful" case.

Into the "unlikely, or proved negative" group fell the 3 cases relegated from the first group because of negative post-mortem examination: Dock (1924); Kennedy, first case (1926); and Harrison and Abernethy, first case (1934); along with Lundholm and Ströman's (1930) case, a one-year-old girl, Michelsen's (1930) case, Richter's (1934) 2 cases, and Pick's case; eight in all.

Clinical Evidence of Endocarditis in these Cases.—The *heart murmurs* in the cases in the "probable" group were: case (1) a systolic murmur at the apex extending round to the axilla and back, along with pericardial friction; case (2) systolic; case (3) soft systolic at apex, faint diastolic in third space and left sternal margin; case (4) systolic and short diastolic; case (5) soft systolic; case (6) systolic over pulmonic area, rough systolic over apex; cases (7, 8, 9) see Appelbaum's remarks below; and case (10) rough systolic and diastolic in aortic area.

In Appelbaum's 3 cases (7, 8, 9) very careful examinations were carried out before a final diagnosis of endocarditis was made. He wrote: "In this study the diagnosis of endocarditis was based on the development of an endocardial murmur or murmurs, particularly if diastolic, which persisted throughout the course of the illness, on the presence of clinical or electrocardiographic evidence of impaired myocardial function, and on the roentgenographic changes in the size and contour of the heart, particularly during convalescence. A progressive rise in the number of bacterial colonies in the blood culture during the active phases of the disease was regarded as corroborative evidence of endocardial infection."

The murmurs in the second and third groups were, when described, systolic or, in one case in the "possible" group and one in the "unlikely" group, pre-systolic. In 4 cases in the last group the murmurs were respectively described as brief, slight, soft and faint. There were no diastolic murmurs in these groups.

Among other reasons for regarding the cases in the first group as probably endocardial infections were: Marfar and Debré's case (1), a girl of 10 years, showed evidence of mitral incompetence. She was regarded by the physicians

as a case of gonococcal endocarditis; but, for reasons which will be given later, is classed here as a meningococcal case; she recovered under meningococcal serum therapy. Bittorf's case (2) had hæmorrhagic nephritis probably due to renal infarction. He died from meningitis; there was no post-mortem examination. Hennell and Wiener's case (3) was ambulatory at first. For 3 weeks he went to work in the mornings, went to bed in the afternoons when his temperature was high, and sometimes worked again in the evenings after it had fallen. He had drenching sweats. He appeared acutely ill on admission after 7 weeks' illness, had heart murmurs, and became increasingly toxæmic and stuporose, with a temperature now more continuously elevated. He died after 9 weeks' illness in spite of serum treatment. They wrote: "Although an acute endocarditis was definitely present, he did not show any sign of cardiac weakness even to the very end." There was no post-mortem examination. Master's cases (4, 5, and 6) all recovered under serum treatment. The first looked acutely ill on admission and was thought to have possibly a meningococcic endocarditis grafted on an old rheumatic lesion. The second had an enlarged heart, but does not seem to have been so ill. The third was acutely ill on admission and had profuse sweats. Appelbaum's 3 cases (7, 8, and 9) all recovered with serum therapy in 7 weeks, 7 weeks, and 5 weeks respectively. The first was a boy of 10. Heinle's case (10) died after 4 weeks' illness. Antimeningococcal serum was not used as the organism obtained from the blood was not identified till after death. There was no meningitis. The final diagnosis was chronic meningococcus septicæmia terminating with acute meningococcus endocarditis of the aortic valve. There was no post-mortem examination.

The case of Stewart-Wallace (1936) in the "possible" group might reasonably perhaps have been included in the "probable" group. A man of 25, he looked ill on admission, and lost weight rapidly. He had a systolic murmur at the apex. The organism was a Type 1 meningococcus. He recovered after 4 months' illness, without serum treatment.

In most of these cases, probable, possible, and unlikely, the course of the illness was at first suggestive of chronic meningococcæmia. Marfar and Debré's patient was an exception, and there was, of course, a primary meningitic phase in Landry and Hamley's case, and early onset of meningitis in Bittorf's case. But nearly all had in the early stages intermittent fever, crops of skin lesions of the papular or nodular, occasionally pustular type, often tender, and quite unlike the petechiæ of the cases of primary meningococcal endocarditis already described. Arthralgia or arthritis was present in 15 of the total 25 cases, and in 5 of the 10 "probable" cases.

The occurrence of drenching sweats did not help very much in the diagnosis in this series. Though present in 2 of the probable cases, and in Stewart-Wallace's case, they occurred also in Kennedy's first case, shown post-mortem to have no endocarditis, and in Richter's 2 cases, in which there was little evidence of endocarditis except for murmurs.

A more important point was the greater "illness" of the patient, sometimes with loss of weight. There was not the interpyrexial "wellness" in these "probable" cases, which is so frequently observed in pure meningococcæmia.

The conclusion therefore is: In these 10 cases of the "probable" group and perhaps in one or more of the cases in the "possible" group, there was either meningococcal endocarditis, or meningococcæmia of a particularly

toxic kind which affected the myocardium and produced murmurs, causing an illness which was for a time more severe than that of typical meningococcæmia. Supposing them to be cases of endocarditis, they differed from those of the proved group in that they suggested not a primary endocarditis, but one supervening in the course of meningococcæmia.

Meningitis, Mortality and Treatment in the Unproved Group.—In the "probable" group of 10 cases there were 3 deaths. Bittorf's patient died with early meningitis, while Hennell and Wiener's and Heinle's fifth case died without meningeal involvement. All the cases in this group were treated with serum except those of Bittorf and of Heinle.

In the "possible" group of 7 cases there were no deaths. There was primary meningitis in Landry and Hamley's case, and meningitis developed in the second week in Appelbaum's "possible" case, and after 6 weeks' illness in Kennedy's third case. Serum was given in all the cases save those of Harrison and Abernethy (second case), and of Stewart-Wallace. Artificial fever therapy was used for Krusen and Elkin's patient.

In the "unlikely, or proved negative" group of 8 cases there were 3 deaths. These were Kennedy's first case in which terminal meningitis developed after 2 years' illness, and Dock's with meningitis occurring after 6 months' illness, while Harrison and Abernethy's first case had chronic nephritis but no meningitis. Serum was given in the cases of Kennedy, Lundholm and Ströman, Harrison and Abernethy, and Richter, first case. Trypaflavin was used in Michelsen's case. Pick's case developed meningitis but recovered with sulphapyridine treatment.

Types of Meningococci obtained in the Unproved Group.—In the "probable" group the organisms from 9 cases were not typed. In one case (Marfar and Debré) it was agglutinated by Dopter's serum and was classed as Group I. Two cases in the "possible" group yielded Type 1 meningococcus (Stewart-Wallace, and Harrison and Abernethy, second case), one an organism agglutinated by polyvalent serum; 4 strains were not typed. The "unlikely, or proved negative" group yielded one Type 2 strain (Harrison and Abernethy, first case), 3 agglutinated by polyvalent serum, one "paranormal," and 3 untyped.

It is a pity that only one of the organisms in the first group was typed; it is not possible to say whether there was an undue proportion of one type in these cases. It is worthy of note that 2 cases in the "possible" group yielded a Type 1 organism.

Discussion.—As a result of the analysis it suggests itself that meningococcal endocarditis may be divided into three classes: (1) that developing during or following primary meningitis; (2) primary endocarditis in which there is early involvement of the endocardium; and (3) endocarditis developing during the course of meningococcæmia.

In the first group death may occur from meningitis, and the presence of endocarditis may only be discovered at post-mortem examination. In other cases there is recovery from the meningitis, and endocarditis may manifest itself later, though it is evident that the process may have begun during the meningitic phase.

Cases of the second group are usually fatal, and show evidence of insufficiency and often infarctions. From the case described by Cutts, Krafft and Willcox it seems that in future some of them may be saved by sulphonamides.

The third group exists rather in the realm of probability than of fact. Evidence for its existence has been given in the foregoing sections. If we accept that the "probable" and perhaps even some of the "possible" cases have endocarditis: Why do some of them recover so easily? Why do not more of them have infarctions? Why do they not more often proceed to valvular insufficiency? Why do they differ so much in their clinical behaviour from cases of primary endocarditis?

It is conceivable that in the cases of primary endocarditis the whole force of the meningococcal attack is concentrated at an early stage of bacteræmia on the valve, while in those developing at a later stage in meningococcæmia there is already dissipation of the cocci throughout different tissues of the body, such as skin and joints. It is probable that in the latter group the body's defences have already been mobilised, and that when the attack on the valve comes it is held more or less in check.

Perhaps the most likely explanation is therefore that primary meningococcal endocarditis takes place when a valve has some defect or weakness such as an old rheumatic lesion or when there is some mechanical reason rendering the valve unduly vulnerable to attack, and that a less severe endocarditis takes place when a healthy valve is attacked during the course of meningococcæmia, with the factors of dissipation of bacterial energies, and of mobilised defences playing their part.

In primary endocarditis the main persisting focus of infection must be the valvular lesion, and the readiness with which cocci or masses of cocci can be shed into the blood stream explains the difference in the clinical character of the illness from that in meningococcæmia; in the latter the persisting focus is presumably more shut off, and escape of organisms into the blood-stream is more intermittent. Presumably in the milder forms of endocarditis occurring in meningococcæmia the main persisting focus is not the valvular lesion, and the clinical course is, for a time at any rate, that of meningococcæmia.

Proved cases of endocarditis occurring in the course of meningitis show the characters of primary endocarditis rather than of those developing in the course of meningococcæmia, but it is evident from post-mortem results as well as from the occurrence of late and fatal sequelæ that endocardial infections may be unrecognised during life. It is impossible to estimate the number of mild infections, unrecognised during the illness, from which there is complete recovery.

Endocarditis due to other Neisseria.—Endres (1925) reported a case of endocarditis and nephritis, proved by post-mortem examination, in which the organism was claimed by Schilf (1925) to be *N. catarrhalis*, and there have been a few other cases of endocarditis believed to be due to this organism. Goldstein (1934) had a case of endocarditis and pericarditis, proved by post-mortem examination, in which the organism was determined to be *Neisseria pharyngis siccus*.

Gonococcal endocarditis is well recognised. It may be mentioned here that the case of meningococcæmia, with probable endocarditis, of Marfar and Debré (1910), a girl of 10 years, was reported by the authors as one of gonococcal infection. The organism from the blood was actually identified, biochemically and serologically, as a meningococcus, and was apparently regarded as a gonococcus purely because there was metritis, and a vaginal discharge containing Gram-negative diplococci. There may, of course, have been two

separate infections. The organism in 2 other cases of meningococcæmic infection was thought, for similar reasons, to be a gonococcus, till proved to be a meningococcus.

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One suggestion in the informative pamphlet* recently issued by the Ministries of Food and Health may be new to doctors treating cases of gastric and duodenal ulcer.

It is the recommendation (Section C) of blackcurrant syrup (with biscuits, rusks or sandwiches) as a mid-morning snack for patients who have recovered from the acute stage of peptic ulcer. Where, because of the patient's distaste for considerable amounts of uncooked vegetables, it is necessary to supplement the vitamin C intake in other ways, blackcurrant syrup is advocated to be taken daily.

Doctors following the pamphlet's recommendations will find in Ribena Blackcurrant Syrup an acceptable and quite economical medium for increasing the intake of natural vitamin C (content: not less than 20 mg. per fluid oz.).

Independent clinical investigations have incidentally shown that Ribena accelerates disappearance of symptoms and assists healing even in acute stages of peptic ulcer.

BOTTLE SHORTAGE: Will doctors kindly instruct patients to return empty Ribena bottles to a chemist?

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* *Diets for Patients with Ulcers of the Stomach and Duodenum.*

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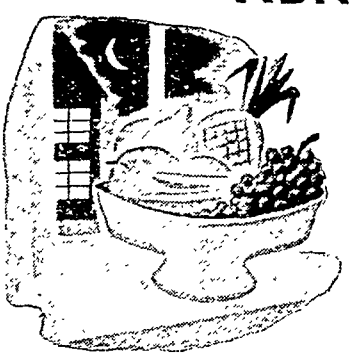

As the war effort is hitting full stride, it brings with it many dislocations of civilian habits which affect the normal routines of normal times.

Not the least important of these disturbing effects is irregularity of bowel action with its resultant symptom complex, loss of appetite, depression, fatigue, listlessness — all of which tend to lower bodily and mental efficiency.

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ANGIER'S
Emulsion

THE MANAGEMENT OF MULTIPLE INJURIES IN AIRCREWS *

By Wing-Commander IAN LAWSON DICK, M.D., F.R.C.S.Ed.

From an R.A.F. Hospital

THREE types of injury result from the hazards of operational flying in war: (1) gun-shot and missile wounds; (2) burns; and (3) fractures and fracture-dislocations.

1. Gun-shot and Missile Wounds

In a paper dealing with aircrew casualties these wounds by themselves need no special mention. They present no inherent problem and have no peculiar feature to distinguish them from similar wounds inflicted under other circumstances. As isolated injuries they are relatively insignificant, and two readily understandable factors aid the surgeon in their repair. There is seldom a long interval between the wounding and the admission of the patient to hospital, and gross contamination of the wounds is not common. Efficient early treatment reduces the incidence of serious infection, and gas gangrene is very rare. Two of the gravest complications of missile injuries are therefore almost eliminated. The main difficulties are found among the second and third types of injury especially when, as so often happens, they are mixed.

2. Burns

In the Royal Air Force the problem of the burn is very specialised and of first-class importance. It is specialised because practically always the same areas are burnt. Even a light layer of clothing affords very considerable protection against burning by flame. The trunk and limbs which are covered by heavy flying clothing are rarely burnt, but the hands and face which are not so protected commonly suffer. Having indicated what areas are affected, I do not need to emphasise further the importance of the problem which treatment presents. Unless the burnt areas heal rapidly with minimal contracture serious disability must result. Even extensive burns of the trunk and upper limbs may heal with quite considerable scarring, but the effect upon the function may be only slight unless joints are involved. This is not so with burns of the hands and face.

The longer an area granulates, especially when it granulates in the presence of infection, the more fibrous tissue is laid down in its base, and the deposition of fibrous tissue in a healing wound inevitably leads to contracture. The problem, therefore, in the treatment of

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 18th May 1944.

burns of the hands and face is that of covering the burnt area with skin without avoidable delay. In addition, in the case of the hands function must be preserved throughout. If joints are opened, tendons destroyed, and prolonged granulation is inevitable, measures must be taken to ensure that the function of the hand is not further impaired by preventable contracture.

When this war began the treatment of burns by the application of tannic acid or some other form of coagulant was almost universal. This was and still is adequate treatment for many burns, though I do not believe that it is the best treatment for any burn. Very early in the war it was realised that the results of the treatment of burns of the hands and face by this method were disastrous and that, especially in the hands, coagulation of the burn could and did produce consequences more serious than those of the original trauma.

The coagulant treatment of burns depends for its success on the maintenance of sterile conditions under the coagulum. Then and then only can it be used without causing harm except in burns of the hands. But burns of the face treated with tannic acid are inevitably infected under the tan from the eyes, the nose or the mouth; and all burns in which there is actual destruction of tissue, so-called " third-degree " burns, must become infected at some stage. In any case there is no good reason for coagulating with chemicals that which has already been destroyed by heat. In burns of the face even without tissue destruction some degree of infection must occur, and treatment should be directed to its control. In third-degree burns of the face and elsewhere controlled infection is a valuable part of the healing process, for without it sloughs separate much more slowly.

Though infection serves a useful purpose while the sloughs are separating, it must be eliminated at the stage of re-epithelialisation of the burn. The recent popularity of the closed plaster treatment of wounds and compound fractures, and the undoubted and amply proved value of this method of treatment for this type of wound, have led to some confusion of thought about its applicability and the indications for its use. It is true that infected compound fractures heal in a closed plaster, and that if drainage is adequate the associated soft tissue wound, benefiting also from the plaster splint, granulates readily; but that is the point: the wound granulates. Granulations grow well in a wound enclosed in plaster even in the presence of infection, and the exuberant heaped granulations which are so produced are a familiar sight. Epithelium will not grow well under these conditions. Growing epithelium thrives best on flat sterile granulations and is inhibited by infection in a wound bathed in pus under a plaster or a coagulum. There is no need to " stimulate " epithelial growth by the use of coloured lotions of great repute but of no proved value. Epithelium will grow with amazing speed if the obstacles to its growth are removed. The usual obstacles are infection and irregular granulations.

Face.—Burns of the face are best treated by daily saline irrigation, if possible in a saline bath, though this is not obligatory, and dressings of sulphonamide powder, tulle gras and saline packs until any slough has separated. As soon as infection is under control the remaining raw areas are covered with a split-skin graft. Thus contracture is minimised, the need for subsequent plastic repair of the face is reduced, and such repair as may be needed is facilitated. Particular attention must be paid to the areas around the eyes, and every possible measure must be taken to minimise contracture here. Contracture around the eyes causes exposure of the cornea, and this in the presence of infection results in corneal ulceration with loss of the eye. The treatment of burns of the face must centre around the preservation of the eyes. In all cases in which the eyes are in danger penicillin is now instilled into the conjunctival sac, and I have seen eyes saved by this means which would otherwise certainly have been lost. This is by far the most valuable single contribution which the introduction of penicillin has made to the treatment of burns.

Hands.—The coagulant treatment of burns of the hands may do dreadful damage even in the absence of infection. Burnt hands must swell, and often the swelling is greater with the lighter degrees of burning. In the hands œdema acts like glue, and unless swollen hands are kept moving serious stiffness will result which may last for months or may even be permanent. Fingers and hands clothed in a glove of inelastic coagulum cannot be moved and must stiffen. Hands should be treated with daily saline baths and with sulphonamide, tulle gras and saline packs bandaged on so that the fingers can be moved and exercised from the beginning to preserve their function. So treated they need never become stiff.

The granulations are covered with a split-skin graft as soon as they are ready to receive it. There is always a temporary deterioration in finger movement after the skin-grafting of a burnt hand. It is directly due to the fact that the hands have to be immobilised so that the grafts may take, and it is soon overcome only because the period of immobilisation does not exceed four or five days.

Coagulants used on burnt hands may cause greater disaster than prolonged stiffness. The unyielding coagulum acts as a tourniquet and strangulates the swollen hand and fingers even to the degree of producing gangrene. Those who wish to read the account of one who suffered the appalling calamity of the loss of his fingers in this way may find it set out in his own words in *One of our Pilots is Safe*. Surely no book ever had a more sadly satirical title. Even if the coagulum does not cause gangrene the vascular supply of the splinted fingers is seriously impaired, and this state of affairs continuing for more than a few days produces what has been aptly described as a " frozen hand." The fingers are spindled, the skin is shiny and atrophic, and there is no more than a shiver of movement in the finger-joints. Though the fingers are still there the hand is functionally useless.

When the burning is so deep as to destroy tendons and open joints,

another consideration must guide the surgeon in his treatment. Severe limitation of movement will result from a burn of this degree, and what movement remains must be facilitated by the functional position of the hand and not hindered by preventable contracture. In the Royal Air Force the hands are usually burnt worst on the dorsum, and the characteristic contracture of a severe burn of the dorsum of the hand fixes the metacarpo-phalangeal joints in hyper-extension. Once this contracture has become established there is no known means of restoring any function whatsoever to the affected digits. The rarer burns of the palm produce a flexion contracture which is equally disabling. Hands thus gravely burnt must be splinted, preferably in plaster, in the optimum functional position with the metacarpo-phalangeal joints in mid-flexion until a fibrous ankylosis occurs. Then the patient is encouraged to develop such movement as he can. It may not be much, but it is useful movement in the position of function and not the pathetic flicker of a subluxated joint.

The rules governing the treatment of burns of the hands are quite simple and are in exact accord with surgical first principles: control infection; promote healing; prevent contracture; above all, preserve function. Unless the hands are in plaster active movements are practised hourly. Patients are encouraged to perform for themselves the everyday routine of life, such as feeding, dressing and lighting cigarettes. Not long ago I saw a new arrival offer a light to a boy with badly burnt hands who was having difficulty with a match. The offer was refused with "Don't you know better than that? Never help a 'burns' patient." That must be the attitude of all who are dealing with patients with burns of the hands. There is no lack of practical sympathy, but it is not openly expressed, and it is always remembered that misplaced sympathy will delay recovery.

3. Fractures and Fracture-dislocations

In contra-distinction to the stereotyped burns of aircrews the fractures and fracture-dislocations which they sustain are characterised by their multiplicity and extraordinary variety. This is understood when the degree of force producing the injuries is remembered, and when it is realised to what terrible stresses machines and men are subjected in aircraft crashes. The horse-power developed by the engine of a single-seater fighter exceeds that of the locomotive which pulls the Flying Scotsman, and the speed of impact in aircraft crashes to-day is seldom less than 100 miles per hour. It is often more. It is not surprising that these accidents produce more than one injury in the same patient, or that the injuries commonly show severe displacement and are frequently compound. They are often associated also with head injury; this may dominate the immediate picture and delay the treatment of other injuries.

These are some of the difficulties. On the credit side of the balance there are two factors which help greatly in the treatment of aircrew

casualties. Firstly, they occur in young fit men whose morale is high. Secondly, they usually come under treatment within a few hours. Thus in the Royal Air Force we have had the opportunity of treating with success combinations of injuries which must under other conditions have proved fatal.

The treatment of a patient with multiple injuries is divided into two phases: (1) the immediate; (2) the remote or definitive. In the immediate phase the general considerations consist mainly in the control of shock, and the local considerations are those of prevention of wound infection and primary reduction and splinting of fractures. The treatment of the fractures themselves occupies a very secondary place in the immediate phase, and care must be taken that it is not given undue emphasis. Definitive treatment is concerned with the management of wound healing, the replacement of skin loss and the accurate realignment of fractures. In this phase all possible methods of fracture treatment should be available. Often the programme which would otherwise be considered most suitable for the treatment of an individual injury is made impossible because of unavoidable delay in starting it, because of infection, or because of other injuries in the same limb or elsewhere.

A. IMMEDIATE TREATMENT—**Shock.**—The treatment of shock may be epitomised very briefly as the use of measures to restore to normal the volume of the circulating blood. As soon as a patient with multiple injuries comes under treatment, a blood-pressure reading is recorded and a plasma transfusion is begun. This blood-pressure reading is not made for diagnosis, for it can be assumed that a patient with one or more major fractures is shocked. It is made to afford a base-line against which further readings can be compared. Plasma can be used without any typing or cross-matching, and is as efficacious as blood in restoring the blood-volume in the initial stages of resuscitation. McMichael has shown that, in the stage of hæmo-concentration, transfusion of up to two pints of plasma not only restores the blood volume but brings again into active use red cells which were stagnant in dilated capillaries.

Massive plasma transfusions are not desirable for three reasons:

(1) A transfusion of more than two pints of plasma causes hæmo-dilution, and then plasma becomes much less effective in controlling shock than whole blood.

(2) The administration of large amounts of plasma is followed in two or three weeks by a very troublesome and intractable secondary anæmia.

(3) Large amounts of blood are lost into the tissues in closed fractures and without any external bleeding. One and a half to two pints of blood may be extravasated into the muscles of the thigh with a closed fracture of the femur.

Blood, therefore, is used for massive transfusions.

Three or four pint transfusions are relatively common, and an empirical limit must not be set to the amount of blood which should be given to any patient. The largest transfusion of which I have had experience was used in the treatment of a dispatch-rider who was gravely injured in a collision with a tank. He was moribund when he reached hospital, and he received two pints of plasma and twelve pints of blood before operation was successfully undertaken. I was recently asked to see a soldier who had suffered an accidental gunshot wound of the leg with a gross compound shattering of the tibia and a closed fracture of the femur on the same side. When I saw him he had been under treatment for about three hours. He was desperately ill, with a systolic blood-pressure of 80 mm. and a diastolic pressure which I could not estimate. There had not been much external blood loss, and he was then having his fourth pint of plasma, which was being used " because it is just as good as blood in pure shock." The surgeon in charge of him was concerned at his lack of response. Not only was treatment based on a false premise but the fact that there was, in addition to what he had lost externally, a blood loss of two pints into the muscles of his thigh had escaped notice. He needed blood, and he needed it urgently. In the following thirty-six hours he had ten pints of blood, and during this time the injured limb was successfully amputated at mid-thigh. He ultimately recovered.

Gravely shocked patients should be lifted and moved as little as possible. They are adversely affected by lifting and should always be taken from the ward to the theatre in bed and not on a trolley. One lift from the bed to the table is enough, and they should be lifted with scrupulous care and gentleness. Any alteration of position of the table or alteration of the tilt of the table itself should also be made very carefully and gradually. Further, severely shocked patients should not necessarily be moved to hospital as soon as they are seen at the site of the incident. A patient may stand a short journey to a nearby place of shelter where he can be given plasma and blood and left to recover till he is fit to move further, when he would have died in the ambulance had he been taken straight away on an hour's journey.

Estimation of Degree of Shock.—The blood-pressure is the most valuable indication of the condition of a shocked patient and of the effect of resuscitation. An estimation of the state of the peripheral circulation by observation of the rate of return of surface blood to the lobe of the ear or the nail bed is a much less accurate indication and is open to wide personal error on the part of the observer. This sign is of little use to the inexperienced, and though it is of some value to those with experience, even they use it only as an adjunct and place by far the most reliance on the behaviour of the blood pressure. I do not believe that any dependable assessment of a patient's condition can be made by counting the pulse or by estimating its " quality " with the finger.

One blood-pressure reading is not enough. Shock is one of the most treacherous and deceitful conditions in the whole of surgery,

and if reliance is placed on one blood-pressure reading alone errors are inevitable. An accurate estimate of the patient's condition can be made only by a determination of whether the blood-pressure is stationary, rising or falling. There is a stage of vaso-constriction in shock when the blood-pressure is high, and sudden and dramatic alterations may happen without warning. A patient, whose general condition did not give rise to anxiety and whose blood-pressure was 140/90, was left without transfusion. Two hours later he was obviously profoundly shocked and his pulse was impalpable. He had been in the vaso-constrictive phase of shock, and the single blood-pressure reading had given an entirely erroneous impression of his condition. In point of fact the slight elevation of the blood-pressure might have roused suspicion, but this indication was missed and a grave degree of shock was not recognised until the point of extreme danger was reached.

Transfusion, therefore, is started immediately, for once the needle is in the vein shock is largely under the control of the surgeon. So that sudden deterioration of the patient's condition may not escape recognition, the blood-pressure is recorded and charted at fifteen-minute intervals while the preparations for operation are being made and every ten or even five minutes during the operation. The medical officer in charge of the case must keep most careful watch so that he may promptly counter sudden worsening of the patient's condition by speeding up the transfusion.

Anæsthesia.—Great importance attaches to the anæsthetic and to the method of its administration. The anæsthetist is a key member of the surgical team. In my opinion there is no field of surgery in which administration of the anæsthetic needs more precise judgment or greater care. The anæsthetist and the surgeon must work in the closest co-operation. It is my practice to discuss with the anæsthetist what I would like to do, to estimate with him what will be possible, and to plan my procedure accordingly. There is always an understanding between us that I shall be entirely guided by him about how long I may continue to operate and that I am prepared to stop immediately at his request.

Type of Anæsthetic.—Spinal analgesia is never used. The drop in blood-pressure which it produces and the fact that its effect once established is not readily reversible combine to make it too dangerous. Many fatalities from the use of spinal analgesia in shocked patients have been recorded, occurring before operation had even begun. Rear-Admiral Gordon-Taylor truly says, "If you want to practise euthanasia in war surgery use spinals."

Local anæsthetics are usually excluded by the technical difficulty of the multiple infiltrations needed and by the potential or actual infection of the wounds, but sometimes regional blocks may be used with advantage. Brachial plexus block is particularly useful both in immediate and in definitive treatment.

Intravenous soluble barbiturates are valuable for induction but

must be used with great care. They act very rapidly and in very small doses in shocked patients as, incidentally, they also do in patients with established sepsis. Pentothal should not be used in a solution of greater strength than 2·5 per cent., and a shocked patient may be completely anæsthetised by 3 or 4 c.cm. of this solution who would ordinarily need 12 or 15 c.cm. of the usual 5 per cent. solution, or about twelve times as much Pentothal.

Gas and oxygen given by an expert anæsthetist with especial care to avoid any increase in tissue anoxia is the best means of maintaining anæsthesia. A little ether or cyclopropane is added if necessary. If an expert is not available, the less experienced anæsthetist is probably safest with ether. This is best given by the Oxford Vapouriser introduced by Air-Commodore R. R. Macintosh.

IMMEDIATE LOCAL TREATMENT.—The most important object of the immediate local treatment of patients with multiple injuries is control of infection. This is effected by two means: (1) by careful and thorough excision of wounds; and (2) by the prevention of skin necrosis due to gross bony displacement.

Wounds.—The principles governing the primary local treatment of wounds have been enunciated many times and do not need further repetition. I would emphasise just one point. As my experience of war wounds grows I become more and more convinced that primary suture is never indicated. I feel very strongly that the introduction of penicillin has as yet added nothing to the arguments in favour of primary closure. I have never seen anything but a little time lost by leaving a wound open. It is easy to do a delayed primary or a secondary suture if the wound remains clean. The ill-advised primary suture of a wound may precipitate grave infection which will endanger life or limb. I now never suture war wounds primarily, however favourable the conditions may appear to be.

Fractures and Fracture-dislocations.—I have already indicated that bony injuries are usually severely displaced. If they are not compound when first seen the skin is often so stretched over the underlying bone that it will necrose in a few hours. This is particularly true of fracture-dislocations of the ankle and foot. In the immediate treatment the displacement should be clinically reduced so that the skin is preserved and the complication of sepsis is not added to the existing lesion. As soon as the skin is safe, further time should not be spent in X-ray check and possibly remanipulation in a gravely ill patient. The necessary adjustments can be made when his life is no longer in danger.

Plaster.—A limb in which there is a fresh or a recently manipulated fracture or a recent wound due either to accident or to operation must not be enclosed in a complete plaster. The plaster must be split in its whole length, and the dressings under it split down to the skin so that reactionary swelling cannot endanger the blood supply of the limb. A patient arrived at a Royal Air Force hospital two days after he was injured. Both legs were in full-length unsplit plasters

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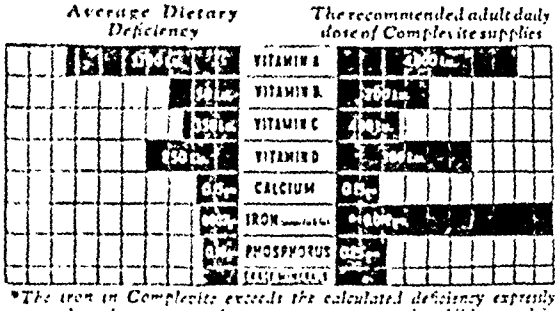

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1 *B.M.J.* 1944, 2, 244.
2 *Brit. Dental J.* 1942, 73, 47.

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and both feet were gangrenous. The plasters were removed at once, but both legs had to be amputated below the knee. His primary injuries were minor closed fracture-dislocations of both ankles and moderate second and third degree burns of both legs.

The following case illustrates most of these points.

R. B., a rear-gunner, was injured when his aircraft crashed on take-off. He sustained a compound fracture of the shaft and a simple fracture of the neck of the left femur, a grossly compound severely comminuted fracture-dislocation of the left ankle and a fracture-dislocation of the right ankle. After he had been given a pint of plasma and two pints of blood he was well enough for some operative treatment, but it was obvious that he could not stand much, and that the operating time available had to be carefully apportioned. Blood transfusion was continued throughout the operation. Anæsthesia was induced with dilute Pentothal (he was asleep when he had had 3 c.cm. of a 2·5 per cent. solution), and maintained with gas and oxygen.

The two ankles were the most urgent injuries, the left because it was grossly compound, and the right because the skin would obviously slough if reduction were delayed more than a few hours. The fracture of the femoral shaft was only slightly compound from within and there was no gross muscle damage.

The left ankle wound was rapidly excised, the displacement was corrected clinically, the wound was packed open with vaseline gauze and a padded split plaster was applied up to and including a transfixion pin which my assistant had meantime inserted through the tibial tubercle. The gross displacement of the right ankle was corrected clinically, making the skin safe from further pressure from within, and a padded split plaster was applied. The thigh wound was excised and packed open. A Thomas's splint was applied to the left lower limb, and the patient was returned to bed with the femur controlled by fixed extension from the tibial pin.

In a few days, when the general condition had improved, the displacement of the femoral shaft fracture was corrected by weight extension and by adjustment of the posterior and lateral splints till adequate alignment had been achieved. Ten days later, at three weeks from the accident, the reduction of the fracture-dislocation of the right ankle was completed by further manipulation with open replacement and screw fixation of the internal malleolus. Complete reduction of the internal malleolus by manipulation alone was not possible because, as so often happens, torn and displaced periosteum was interposed between the fragments.

Five days later the fracture of the femoral shaft was already sticky, and the realignment of the limb was completed. The patient was slung in a Hawley table and the two femoral fractures were accurately aligned under X-ray control. A double plaster spica was applied down to and including the tibial tubercle pin. The plaster was removed from the left leg and foot below the tibial pin. The compound wound

was clean and granulating; it was redressed with sulphanilamide and tulle gras. The residual ankle displacement was corrected clinically and radiologically till the foot lay squarely under the tibia in good weight-bearing alignment and the foot and leg were again immobilised in plaster which extended up to meet the upper plaster. Now as the ankle wound heals the joint may fuse spontaneously in satisfactory position. If fusion is not sound, an operation to produce firm ankylosis is relatively simple. The femoral fractures will not need any further adjustment and will be held in plaster till they are firm.

The primary operative treatment of this patient took only forty-five minutes, but by the time it was finished his condition, in spite of blood transfusion, had begun to deteriorate and he would not have stood much more. In the definitive treatment the manipulative and operative reduction of the right ankle occupied one hour and a quarter, and the realignment of the left lower limb and application of plaster took nearly four hours. But these adjustments were undertaken on a patient who had recovered from his shock and was in good general condition. They upset him hardly at all.

B. DEFINITIVE TREATMENT—**Wound Healing.**—When there is no skin loss, wounds of almost any size will heal with remarkable rapidity under a closed plaster if infection is adequately controlled. Granulations soon fill up any defects in a properly excised wound, and in a very short time what had been a saucerised cavity is flush with the skin surface under the plaster. Final healing soon follows. If infection persists in such a wound, it is maintained either by inadequate drainage of the wound and consequent pocketing, by the sequestration of infected bone, or by a retained foreign body. The wound needs further exploration with provision for free drainage and the removal of any foreign body or separated sequestrum. In this connection it must be remembered that not all foreign bodies in wounds are radio-opaque, and that an X-ray which does not show a sequestrum or a piece of metal does not exclude the presence of a piece of wood, cloth, leather or perspex. But if infection is controlled a wound will granulate rapidly inside a closed plaster up to the skin level and will then heal if there has been no skin loss.

Skin Replacement.—When skin has been lost the picture is different. Any tissue loss under the skin is made good by granulations which fill the defects and contract into a firm scar, but until the granulation tissue is covered with skin the wound is not healed. It has already been noted that increased fibrosis and consequently greater contracture are a direct result of prolonged granulation. There is also another disadvantage connected with delay in wound healing when there is an associated fracture, for any definitive operation to an underlying or neighbouring fracture must wait till the wound is healed. It is most tantalising to have to watch a fracture which is not amenable to any other treatment than operation become more and more difficult to handle because operation must be postponed.

Again, therefore, the problem of promoting rapid healing of a wound arises, and again, as in the burn, the answer lies in the control of infection and the replacement of lost skin by a skin graft. Usually quite simple forms of skin-grafting, which are well within the competence of the surgeon without special training in plastic methods, are enough. When flaps or pedicled grafts are needed, the aid of the plastic surgeon should be sought. For wounds of the trunk or limbs pinch grafts or " postage stamp " grafts of split skin are used. These are by far the easiest and safest methods of skin replacement, and a sheet of split skin (a very much more difficult graft to cut and implant) has only a cosmetic advantage over them. Split skin grafts the size of the area to be covered are used on the face, but pinch grafts or " postage stamp " grafts may be used with advantage anywhere else.

Just as in the case of a burn defect, epithelium will grow only over flat uninfected granulations, and its growth is inhibited by pus and by irregularities in the surface of the granulations. The wound should be covered in plaster till the granulations are flush with the surface. Then the raw area is prepared for the reception of skin by exactly the same method as that used in the treatment of burns. The wound is irrigated daily with saline, preferably in a saline bath, and dressed with sulphonamide, tulle gras and saline packs till the granulations are ready to receive new epithelium. This stage is reached when the granulations are flat, pink and shiny, when there is little or no purulent discharge, when the culture shows no growth of hæmolytic streptococci or of staphylococcus aureus, and when the new epithelium can be seen creeping in from the edges of the defect. This last is the best indication of all. If skin is growing over the granulations then a skin graft will take without trouble.

The rapidity with which skin defects heal, when treated in this way, has to be seen to be believed. Wounds, which are indolent and in which it looks as though healing had come to a standstill, can be changed in a very short time into responsive healing areas, and very large defects can be reclothed with skin by pinch grafting.

J. E. was an air-gunner whose horribly mangled leg was almost completely severed in an aircraft crash. He had also a severe fracture-dislocation of the spine, and a formal amputation of the limb was out of the question. The removal of the leg was rapidly completed through the fracture of the tibia without any attempt to fashion flaps, and the stump was enclosed in plaster. When his spinal fracture had been reduced and immobilised in an extension jacket the plaster was removed from the stump, the granulating area was prepared with daily saline irrigations, and pinch grafted. The subsequent amputation at the site of election in the thigh was safely made through sound skin and above a healed wound.

E. S. was injured by a heavy vehicle which ran over his leg and degloved an encircling area about a foot wide just below the knee. He was treated in another hospital for a month and came to us with an extensive grossly infected wound which showed no sign of healing.

After ten days of saline bath treatment the area was pinch grafted and seven weeks later it was all but healed.

The method can also be used on a wound under plaster by cutting a window. Some considerable ingenuity is often required of the nursing staff, but I have yet to see a wound in which the method was indicated and was found to be impossible because of technical difficulties.

When the defect involves a joint, a weight-bearing surface like the heel, or an area where tendons are superficial like the back of the hand, a whole-thickness flap of skin must be used to take the strain of constant movement or weight-bearing without breaking down, and to prevent the adhesion of tendons to the scar. Skin defects over the tibia may need a whole-thickness replacement because they often heal very slowly and with a very unstable scar, but even these wounds can be healed in the first instance by pinch grafts if for any reason the immediate application of a pedicled flap is not possible. Flaps may be used in two ways:

(1) by immediate application to a fresh wound, particularly an abdominal flap to a wound of the hand;

(2) a delayed flap such as a cross-leg flap to replace an unstable scar of the tibia.

These are not simple procedures and should be left to the surgeon with special plastic training.

Bone and Joint Injuries.—The treatment of these follows the ordinary lines and is unusual in aircrew injuries only in the severity and multiplicity of the deformities which have to be corrected. Massive bone grafts are often needed to replace lost bone or to provide internal fixation for a fracture the alignment of which could not be controlled by external splints and which could not be treated by early operation because of a wound. A bone graft is essential for the first of the two purposes; it is much better than a metal plate for the second, for it promotes union in addition to providing internal fixation of the fracture.

A. M. lost 4 inches of his lower femoral shaft in a crash. The wound healed cleanly after excision and delayed primary suture, and the length and line of the limb were held by extension and splints till a slender involucrum bridged the gap. This was then reinforced by a massive onlay graft from the tibia together with a graft of iliac bone to encourage more rapid bone regeneration.

C. A. had compound fractures of both bones of the right forearm and humerus, a plateau fracture of the right tibia, a simple fracture of the left femur, and a compound fracture of the left tibia and fibula. The forearm fractures could not be controlled by any means other than open operation and internal fixation, and this was not possible till fourteen weeks after injury. Then with great difficulty the displacement was reduced and the radius was fixed with an onlay bone graft. During the operation the humerus was accidentally refractured. As he was already in a hip spica, a thoraco-brachial spica in addition was out of the question, but the necessary fixation of the humerus was

provided by joining the arm cast to the body of the hip spica with plaster struts. The refracture of the humerus healed in anatomical alignment in six weeks.

Fractures of the Spine.—The variety of the combinations of fractures which are seen in injured aircrews is almost endless, and I make no attempt to cover the whole field, but one common type of injury must be mentioned—fracture of the spine. Specific search must always be made for injury to the vertebral column occurring alone or as an associated lesion in patients involved in aircraft crashes even when no complaint is made of pain in the back. Also, the spines of patients with fractures of the os calcis or astragalus, no matter how they were injured, should always be examined as a routine. Severe pain in the foot often masks minimal discomfort in the back.

A. B. was a physical training instructor who wished to become a paratrooper. He was accepted for training and came to see me after he had completed his initial course of jumps. He was complaining of "a pretty constant ache in the back." He had had this for some time but "had not liked to complain about it" lest he was taken off training. On clinical examination I found a tender lumbar kyphos, and X-ray showed a compression fracture of the first lumbar vertebra. Further questioning elicited the history that he had landed heavily from his first jump and had "jarred his back." He had done five subsequent jumps with this compression fracture of the spine. A complaint of pain in the back after an aircraft crash or a parachute descent must always be thoroughly investigated.

R. A. was admitted from another hospital with a fracture dislocation of the talus. He did not make any complaint of pain in the back, but he was found to be tender on pressure over the lumbar spine and X-ray showed compression fractures of the bodies of three lumbar vertebræ.

I have already made reference to J. E.'s spinal injury when I discussed his leg. On admission to hospital he was gravely shocked, but when he became co-operative enough to be examined he was found to have a tender lump in the lumbar region and X-ray showed a gross fracture-dislocation of L. 1 on L. 2. A spinal extension jacket was applied as soon as he was well enough and before any local treatment to the primary amputation stump was begun. Later when the secondary amputation stump was healed the spine was fused.

There may be an obvious, gross and dramatic injury elsewhere, but the spine of a patient injured by severe violence must always be examined before a course of treatment is planned.

And so I finish. I have tried to present a broad picture and have not entered into great detail on any one point. Maybe I have been too discursive. But I have failed in my object if I have not shown that the management of multiple injuries in aircrews is, if I may slightly modify the words of Robert Louis Stevenson, "a task for all that a man has of therapeutic skill and delicacy."

INVESTIGATIONS ON VITAMIN A CONTENT OF HUMAN BODY FLUIDS

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To understand the metabolism of a vitamin it is important to know the vitamin content of different organs of the body and the body fluids. The present knowledge of vitamin A metabolism in the human body is far from being complete. We know comparatively well the vitamin A content of some of the organs. This is especially true in respect of the liver, which plays an important part in vitamin A metabolism, being the storehouse and the place of conversion of carotene to vitamin A (Moore, 1932; Wolff, 1932, etc.).

We have also a comparatively good knowledge of the vitamin A content of the blood in different conditions of health and disease. The problems connected with vitamin A secretion in human milk have also been thoroughly investigated (Chevallier and coll., Friderichsen and With). There is, however, only scanty or incomplete knowledge about vitamin A content of body fluids other than the blood, such as urine (Lawrie, Moore and Rajagopal).

In a previous paper one of us (Tomaszewski) gave the results of an investigation of vitamin A excretion in urine. In healthy people the urine does not show any traces of the fat-soluble vitamin A even after large doses of vitamin A. But in certain pathological conditions such as kidney disease, liver disease connected with damage to the reticulo-endothelial system, some infective diseases accompanied by high fever, etc., vitamin A may be excreted in the urine in quite large amounts.

In connection with this work on urinary excretion of vitamin A, the question arises whether and in what conditions there is any vitamin A in other body fluids. A further question arises as to whether there is any connection between urinary excretion of vitamin A and the appearance or concentration of vitamin A in the fluids.

This problem has already been investigated by some previous authors, but up to now the results are very scanty and to a certain extent confusing. We thought it would be useful to review the whole problem and to make a more detailed study of this subject. A series of investigations was, therefore, performed on pleuritic, ascitic, pericarditic, amniotic and cerebrospinal fluids.

The investigations have been carried out on the clinical material available from the various wards of the Royal Infirmary in Edinburgh, for which we are indebted to the Chiefs of these particular wards.

Method

The examination of body fluids was made on 100 c.c. of the sample to which 50 c.c. of alcohol were added, and an extraction was made with 100 c.c. of petrol ether. The extract was saponified with 3 per cent. potassium hydroxide and washed twice with an equal amount of distilled water. To remove the traces of water, anhydrous sodium sulphate was added to the extract. After filtration and partial evaporation the carotene, if any, was estimated in the petrol solution. After complete evaporation the rest was dissolved in water-free chloroform, and vitamin A was estimated by Carr-Price colour reaction with antimony trichloride. For quantitative estimation of corotene and vitamin A the photoelectric colorimeter (Spekker) was used. Vitamin A values are given in international units (IU per cent.) and carotene in micro-grams (γ per cent.).

In addition, in nearly all the fluids total protein was estimated by the micro-Kjeldahl method to see whether there was any correlation between the vitamin A content and the amount of protein. This was done in the Clinical Laboratory of the Royal Infirmary, Edinburgh, for which our thanks are due to Dr C. P. Stewart. The examination of urine was made in the same way as the fluids with 100 c.c. samples. The details of the technique and the references are given in the paper on vitamin A excretion in urine (*Edin. Med. Journ.*, 1942, 49, 375).

In some of the cases only one estimation was made; in others there were repeated examinations of fluids and urine. Some of the examinations were made on post-mortem samples of fluids. This was the only way to obtain all the possible fluids from the same case for comparison. In some cases "saturation" tests with oral doses of vitamin A were performed to discover whether there is any influence of vitamin A intake on the vitamin content of the fluids.

Results

Pleuritic Fluid.—Most of the examinations were performed on pleuritic fluids as being most easily available. In some of the positive as well as the negative cases repeated examinations of fluid and urine were made in order to show any change during the course of the disease.

Altogether 25 cases were investigated. The age varied from 10 to 84 years, and the underlying diseases were different. Out of this group 10 were tuberculous pleuritis, 7 neoplastic lung diseases, 4 congestive heart failure, 1 carcinoma of the stomach, 1 perforated stomach ulcer, 1 pleuropneumonia, 1 pyopneumothorax.

The results were as shown on p. 76 (Table I).

It is evident from this table that vitamin A is present in the great majority of cases without regard to the underlying disease. In nearly all the cases of tuberculous pleurisy and neoplastic lung diseases, exudates show the presence of vitamin A. As regards the amount of vitamin A, the neoplastic lung diseases seem to have the highest values. It is also evident that there is no relation between any particular disease group and vitamin A content.

In order to find whether the negative cases can give positive results in later periods we investigated at intervals of a few days the negative

cases of congestive heart failure. In none of the examined samples was there a change from negative to positive.

As the table shows, there is no special relation between the appearance of vitamin A and the total protein content of the fluids. Positive results have been found in fluids of high protein content as well as in those of low protein content. In regard to carotene, the majority of the cases with positive vitamin A results show also a trace or a small amount of that substance.

TABLE I*

Name.	Age.	Diagnosis.	Urine. Vitamin A in IU per cent.	Pleuritic Fluid.		
				Carotene in γ per cent.	Vitamin A in IU per cent.	Total protein in grams per cent.
P.G.	45	Tuberculous pleurisy	...	4·0	10·0	...
M.B.	37	" "	0	2·0	6·0	4·80
P.B.	30	" "	5	2·0	5·5	2·60
J.M.	31	" "	0	2·0	0	3·49
J.H.	31	" "	0	2·0	3·0	4·38
E.H.	28	" "	0	0	8·0	...
M.D.	26	" "	0	0	2·0	...
P.M.	17	" "	tr.	0	12·0	5·33
G.R.	35	" "	0	2·0	3·0	...
F.F.	25	" "	0	2·5	2·5	...
N.T.	84	Bronchial carcinoma	0	23·0	29·0	9·00
O.L.	73	" "	7	3·0	12·0	4·36
N.B.	57	" "	0	3·5	19·0	4·76
J.R.	72	" "	0	6·0	18·0	...
M.D.	59	" "	0	0	4·0	5·11
P.G.	55	" "	tr.	1·5	9·0	...
J.T.	32	Mediastical sarcoma	0	8·0	9·0	3·61
L.B.	50	Carcinoma, stomach	0	0	0	4·00
J.A.	43	Congestive heart failure	0	0	0	2·49
R.W.	47	" " "	0	0	0	4·80
J.B.	64	" " "	...	11·0	14·0	...
A.D.	45	" " "	...	4·0	4·5	1·50
A.J.	45	Pleuropneumonia	12	2·5	1·0	4·08
G.B.	10	Pyopneumothorax	0	17·0	...	4·71
J.B.	45	Perforating ulcer, stomach	...	7·0	8·0	4·44

* 0 denotes negative result; ... analysis not performed.

There is no relation between vitamin A content in fluid and urine. Positive results for vitamin A were obtained in cases where the urine result was negative as well as in those where it was positive. The high vitamin A value (12 IU per cent.) of urine in the case of pleuropneumonia is characteristic for pneumococcal infection, as was shown in our previous investigations on urinary excretion of vitamin A.

Ascitic Fluid.—Altogether 13 cases were investigated. The age of the patients varied from 10 to 50 years. Out of the 13 cases, 5 were liver cirrhosis, 2 carcinosis of the peritoneum, 3 congestive heart failures, 1 nephrosis and 1 tuberculous peritonitis, 1 acute peritonitis. The result is given in Table II.

Out of the 13 cases, 12 showed vitamin A in ascitic fluid. In all the positive cases carotene was also found. There is no relation between

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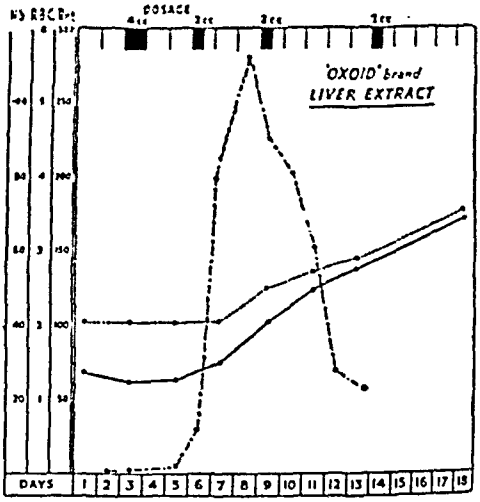

KEY TO GRAPH.

..... *Haemoglobin per cent.*
——— *Red blood corpuscles in millions.*
—·—·— *Reticulocytes per 100 red cells.*

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the content of vitamin A in ascitic fluid and in the urine. Most of the cases gave negative results in urine. There is also no relation to the total protein content of the fluids.

TABLE II

Name.	Age.	Diagnosis.	Urine. Vitamin A in IU per cent.	Ascitic Fluid.		
				Carotene in γ per cent.	Vitamin A in IU per cent.	Total Protein in grams per cent.
M.C.	45	Liver cirrhosis	0	3·5	7·0	3·68
J.C.	50	,, ,,	0	3·5	2·5	...
M.G.	45	,, ,,	3·5	4·5	1·0	0·64
M.H.	52	,, ,,	0	0	0	0·63
D.C.	43	,, ,,	0	4·5	32·0	4·09
A.L.	56	Peritoneal carcinosis	0	13·0	10·0	5.11
J.T.	48	,, ,,	0	5·0	10·0	4·05
G.G.	56	Congestive heart failure	0	...	20·0	...
M.P.	64	,, ,, ,,	0	11·0	8·0	...
A.D.	45	,, ,, ,,	...	3·5	12·0	2·29
A.R.	10	Nephrosis	tr.	2·7	4·0	0·30
M.A.	16	Tuberculous peritonitis	0	4·0	8·0	...
W.J.	58	Acute peritonitis	...	2·5	6·5	2·54

In the nephrotic case a saturation test was made with vitamin A to see whether there is any influence on the vitamin A content in the fluid. Large doses, namely 35,000 IU daily, were given orally during four weeks. Table III shows the results obtained after the administration of vitamin A. The administration of vitamin A began on the 2nd of November.

TABLE III

Case of Nephrosis

Date.	Urine Vitamin A in IU per cent.	Ascitic Fluid.		
		Carotene in γ per cent.	Vitamin A in IU per cent.	Total Protein in grams per cent.
11.10.43	tr.	3·5	3·0	0·30
1.11.43	tr.	2·0	3·0	0·36
20.11.43	8·5	3·0	7·5	0·41
30.11.43	6·0	4·5	14·2	0·40

There is a marked increase in vitamin A content in the ascitic fluid and in urine after large doses of vitamin A.

Cerebrospinal Fluid.—The cerebrospinal fluid of 10 patients was investigated. The age of the patients varied from 14 to 64 years. Of the 11 cases, 4 were cerebral tumours, 2 tuberculous meningitis, 3 subarachnoid hæmorrhage, 1 congestive heart failure, 1 postmeningitic state (meningococcus).

In 2 out of the 11 cases drainage of the cerebrospinal fluid was performed.

The amount of fluid used for investigations varied from 10 to 20 c.c.

Only in cases of cerebrospinal drainage were we able to use 100 c.c. of fluid for examination. The results are given in Table IV.

It is evident that only those cases where cerebrospinal drainage was performed showed positive results irrespective of the underlying disease. All other cases were negative.

The question arose as to whether the positive results obtained were due to the large amount of fluid used for examination, or whether the drainage caused in some way the passage of vitamin A into the fluid. The amount of fluid is certainly of importance. That this was so was observed in one of the cases (M. F.) where the first investigation made on 15 c.c. was negative. When a few days later 100 c.c. were used for the test some traces of vitamin A were found. We found, however, that the amount of fluid is of importance only in cases with very low vitamin A content.

TABLE IV

Name.	Age.	Diagnosis.	Urine. Vitamin A in IU per cent.	Cerebrospinal Fluid.		
				Carotene in γ per cent.	Vitamin A in IU per cent.	Total Protein in milligrams per cent.
A.D.	35	Cerebral tumour	tr.	0	0	80
A.N.	38	,, ,,	0	0	0	...
M.D.	30	,, ,,	0	0	0	...
R.R.	44	Cerebral tumour, drainage	tr.	0	7	90
M.F.	57	Post-meningitis, drainage	0	0	2	...
T.L.	16	Tuberculous meningitis	0	0	0	150
S.K.	14	,, ,,	0	0	0	...
P.M.	64	Congestive heart failure	0	0	0	...
C.B.	31	Subarachnoid hæmorrhage	0	0	0	...
M.R.	27	,, ,,	0	0	0	...
M.S.	52	,, ,,	0	0	0	...

To elucidate the question of the influence of the amount of fluid used for investigations, we tested a composite sample of 100 c.c. cerebrospinal fluid taken from about twenty patients suffering from different diseases. The result was negative. It seems, therefore, that the amount of fluid used for investigation is not the most important factor, but rather that the drainage itself has something to do with the appearance of vitamin A in the cerebrospinal fluid.

Amniotic Fluid.—Six samples of amniotic fluid were investigated from women of ages between 19 to 30 years. Four of them were at full term and two had hydramnion in the sixth and seventh months of pregnancy. The protein content varied from 0·18 to 0·90 gram. per cent. The results are presented in Table V.

Two out of the 6 cases showed vitamin A in the fluid. The positive results in the fluids were not connected with the appearance of vitamin A in urine, as both the positive cases showed negative results in the urine. On the other hand, one positive urine case showed a negative result in the amniotic fluid.

Of the 2 positive cases one was a hydramnion and the other a

full-term pregnancy. It might seem that the condition of hydramnion may favour the passage of vitamin A into the fluid, but the second case of hydramnion was negative. It seems, therefore, that a positive

TABLE V

Name.	Age.	Diagnosis.	Urine. Vitamin A in IU per cent.	Amniotic Fluid.		
				Carotene in γ per cent.	Vitamin A in IU per cent.	Total Protein in grams per cent.
M.T.	19	Full term	0	0	0	0·18
H.H.	21	,, ,,	0	0	4	0·46
A.P.	23	,, ,,	0	0	0	...
M.J.	25	,, ,,	tr.	0	0	0·90
R.D.	24	Hydramnion	0	0	0	0·63
J.R.	30	,,	0	0	5	0·24

result is not bound with greater production of amniotic fluid. The number of investigations is, however, too small to draw any definite conclusions.

Comparison of Different Fluids.—We also compared different body fluids from the same case with regard to vitamin A content. For this purpose we investigated two post-mortem cases. These were cases of congestive heart failure with much effusion into the body cavities. We examined the pleural, peritoneal, pericardial and cerebrospinal fluids. The results of this examination were as follows (Table VI) :—

TABLE VI

Post-mortem fluids

Fluids.	Case 1.		Case 2.	
	Carotene in γ per cent.	Vitamin A in IU per cent.	Carotene in γ per cent.	Vitamin A in IU per cent.
Pleuritic . . .	11	14	4·0	4·5
Ascitic . . .	11	8	3·5	12·0
Pericarditic . .	12	9	14·0	6·0
Cerebrospinal . .	0	0	...	...

Further investigations of this kind would be required to determine whether vitamin A appears equally in all the fluids in certain pathological conditions, or whether there is a greater amount in some.

Discussion

As the tables show, in all the investigated fluids, pleuritic, ascitic pericarditic, cerebrospinal and amniotic, vitamin A and carotene can be found. Vitamin A appears fairly regularly in pleuritic and ascitic fluids, while out of the amniotic and cerebrospinal fluids only certain cases show vitamin A to be present.

The question now arises why in certain conditions vitamin A appears in body fluids, and what is its significance.

It would seem that in the so-called physiological fluids—cerebrospinal and amniotic—the appearance of vitamin A is exceptional. Only under certain circumstances vitamin A may appear in these fluids. No conclusion was arrived at as to the conditions for and the mechanism of the entry of vitamin into the fluids.

The case seems to be different with regard to the pathological fluids. There is no doubt that the great majority of pleuritic and ascitic fluids show vitamin A and carotene. The appearance of those substances must be considered as the rule rather than the exception. The amount of vitamin A in the above-mentioned fluids was not very great. It varied from a trace to 29 IU per cent. in pleuritic fluid. The average was, however, much lower than the latter figure. This is a small amount in comparison with the blood content of vitamin A, where the average is well over 100 IU per cent. The carotene values were also very low, generally in the region of few γ per cent. The normal values of carotene in blood are, according to Yudkin, in the range of 50-241 γ per cent.

In all the fluids investigated no direct relationship between vitamin A content in fluids and in urine could be detected. As a matter of fact, the majority of positive cases showed a negative reaction in urine. There were also cases showing vitamin A positive urine reaction, with negative fluid results. Neither was there any connection between the vitamin A positive reaction and the amount of total protein in the different fluids.

Kaufmann and Drigalski investigated the problem of vitamin A in body fluids. No vitamin was found in the stool, urine or sweat. The examination of bile in 5 persons as well as the investigation of 350 grams of gall-stones did not reveal any vitamin A. They examined the cerebrospinal fluid of 35 persons with negative results. Out of five ascitic fluids two were found to be positive. They found also positive results in pleuritic exudates. The numbers of positive results for body fluids obtained by these authors seem to be smaller than those obtained by us.

Boller, Brunner and Grant also found vitamin A in the transudates and exudates of body cavities. Their results, however, differ somewhat from ours. They found a correlation between urinary excretion of vitamin A and vitamin A positive fluids. Similar results were described by Grant in a separate paper. They investigated also the duodenal juice, and found in normal conditions as well as after large doses of vitamin A that the result was negative. The examination of stools gave negative results for vitamin A, but carotene and carotenoids were found to be present. The pleural reactions in connection with vitamin A reserves in the liver have been studied by Chevallier and co-workers.

The problem of vitamin A in amniotic fluid is of interest as it might permit the better understanding of the vitamin A metabolism

of the fœtus. Some investigations on this problem have been made by Gaethgens. On examining 28 placentas he found in nearly all the cases vitamin A and carotene. The placenta seems to be a storehouse of vitamin A and carotene. The amount of vitamin A and carotene in the placenta varied with the amount of these substances ingested. These reports on vitamin A and carotene metabolism in human fœtus differ somewhat from the investigations of Wendt, who did not find vitamin A in the placenta. Carotene and sometimes vitamin A were found by him in the blood of the umbilical cord. The amounts were lower than in the blood of the mother. Gaethgens found also vitamin A and carotene in the liver of the fœtus. It seems that carotene can be transformed into vitamin A in the fœtal liver.

Small amounts of carotene and vitamin A were found by Gaethgens in amniotic fluid mostly in cases which had some addition of meconium. Therefore this author suggests that vitamin A can probably be excreted through the wall of the fœtal digestive tract and later to the amniotic fluid. Nothing can be said as to whether vitamin A in the amniotic fluid plays any vital rôle or whether its presence is without significance.

Some contribution to the problem of vitamin A levels in maternal and fœtal blood plasma has been recently made by Byrn and Eastman.

Up to the present time no explanation has been made of a physico-chemical mechanism which would promote the passage of vitamin A and carotene into the body fluids in certain pathological conditions. Lawrie, Moore and Rajagopal found that vitamin A was accompanied by protein and lipoid in pathological urines. The ratio of vitamin A to lipids was 23 to 200 IU mg. The form in which vitamin A appears in human blood was investigated by Działoszyński, Mystkowski and Stewart. From their results it would appear (data to be published shortly) that vitamin A occurs in human blood in some sort of association with a plasma protein, probably serum albumen, cholesterol and lipoids. It could be assumed that the " fat-soluble " vitamin A appearing in other body fluids might also exist in certain associations with protein and other substances, but to support this view further work must be undertaken.

The question must be answered as to what extent the saturation of the body with vitamin A contributes to its presence in the fluids. There must undoubtedly be some connection between the vitamin A content of the body and the amount of vitamin A in the body fluids. Some evidence for such influence of saturation with vitamin A is given in the nephrotic case (Table III). Some of the negative results obtained may probably be due to the scarcity of vitamin A reserves in the body. Kaufmann and Drigalski found that negative cases of ascitic fluids could be changed to positive by giving large doses of carotene.

We have investigated only five fluids, namely, pleuritic, ascitic, amniotic, cerebrospinal and pericarditic. Further investigations would be required to see whether there is any vitamin A in other

pathological body fluids such as in the fluid of the joints, of neoplastic cysts, etc. We have found vitamin A and carotene in the fluid of a hydatid mole.

SUMMARY

Investigations were made on vitamin A content in pleuritic, ascitic, pericarditic, amniotic and cerebrospinal fluids. The fluids have been examined for vitamin A, carotene and total protein. In most of the cases the examination of urine for vitamin A has also been made.

In the pathological fluids vitamin A is quite a common finding. Out of 25 cases of pleuritic fluid vitamin A and carotene have been found in 21. Positive results were also obtained in 12 out of 13 ascitic fluids investigated. Vitamin A has also been found in 2 pericarditic fluids. There was no difference between exudates and transudates in regard to vitamin A content. Positive results could be found in both. The amount of vitamin A in the fluids varied from trace to 32 IU per cent.

The cerebrospinal fluid seems as a rule to be vitamin free. Only in cases of cerebrospinal drainage were the results positive. As regards the amniotic fluids, 2 cases out of 6 showed vitamin A.

There was no direct relation between the total protein content of the fluids and the presence of vitamin A. Equally there was no connection between the excretion of vitamin A in urine and the content of vitamin A in the fluids.

Little is known about the way in which vitamin A and carotene pass in certain cases into the body cavities. At present nothing can be said as to the significance of the vitamin A appearance in the fluids.

We wish to express our thanks to Dr C. P. Stewart for the technical help and facilities in the laboratory and for advice in connection with our work.

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WILSON'S DISEASE

By A. J. GLAZEBROOK, M.B., B.S.

From the Department of Clinical Medicine, University of Edinburgh

WILSON'S Disease is a clinical rarity. A study of it, however, brings in questions relating to dysfunctions of the liver, their causation and their effects, and thus the syndrome of hepato-lenticular degeneration becomes of greater interest than its occurrence would otherwise warrant.

The ætiology of this condition is still obscure. Wilson himself advanced the theory that the changes in the brain are produced by disease of the liver, and his view is supported by Braunmühl (1930), Kehrer (1930), and more recently by Waggoner and Malamud (1942). Three other theories have been put forward: (1) that the primary disturbance occurs in certain vegetative centres of the brain, resulting in disease of the liver (Boenheim, 1920; Nayrac, 1924); (2) that the disorders of brain and liver are both expressions of a heredo-degenerative process or abiotrophy (Hall, 1921; Bielschowsky and Hallervorden, 1931); and (3) that an underlying constitutional anomaly of metabolism is responsible for the changes in both organs (Rossle, 1930).

CASE 1.—A boy aged 17 was admitted suffering from torsion spasms. There was a history of "encephalitis" at the age of 10, when he had become a little stiff and slow in speech, and complained of shooting pains in the legs.

The illness slowly progressed over the years, with development of dysarthria and a tendency to dribble saliva. Coarse limb tremors and difficulty in gait gave way to rigidity and contracture, and recently he had become bedridden and completely anarthric.

The torsion spasms set in when he was 15 years old. Often precipitated by emotional upsets, they were controllable to some extent by phenobarbitone.

Neither mental deterioration nor emotional lability had been noticed, and there was no history of jaundice.

On Examination.—He presented a striking picture of striatal rigidity, with head retraction and "lead-pipe" fixation of the arms in flexion and of the legs in extension. Painful torsion spasms occurred frequently. Completely anarthric and unable to write owing to muscle rigidity, he could make his wishes known well enough by pointing to an alphabet he carried, written on a piece of paper.

Kayser-Fleischer rings were present in both eyes, and the liver dulness was much diminished.

Galactose and lævulose tolerance tests showed hepatic insufficiency.

Dysphagia appeared and progressed. Death from broncho-pneumonia occurred, but post-mortem examination was not possible.

Heredo-familial Factors.—The interest of this case lies not in the clinical findings but in the family history.

The paternal grandfather died of "cancer of the liver" and the grandmother of "dropsy."

All the father's brothers died in infancy and childhood except two. These survived to die aged 29 and 32 of a "shaking disease," diagnosed in each case as encephalitis.

The father was admitted to hospital in 1925, at the age of 22, and the account which follows is taken from hospital notes.

He complained of "shakiness" which had set in nine months before his younger brother's death. He had previously been well except for long-standing headaches and obstinate constipation.

On examination a coarse tremor of both arms, tongue and eyelids was present, abolished by voluntary movement. The gait was good, save that the right arm was held rigidly flexed, instead of being swung, on walking. Hippus was present in both pupils, but there were no other neurological signs, and the serological findings were normal.

He was readmitted to hospital several times over the next few years. The disease progressed with development of an open mouth, salivation, dysarthria, stiffness of arms and legs and increasing tremor of both arms.

"Fits" set in towards the end of his illness. These consisted of rotatory movements of the arms and legs, and the attacks lasted from 3 to 7 minutes.

Two years before his death in 1929 at the age of 25 he became completely anarthric and bedridden. He died at home and no post-mortem examination was carried out.

Besides the patient already described, this man had one other son who died in infancy. His daughter is now alive and well, aged 20.

It seems that the father and son were both affected with lenticular disease, and probably so were the father's two brothers. The diagnosis of Wilson's disease is well supported by the clinical findings, in spite of the absence of pathological confirmation.

CASE 2—*Copper Findings.*—Another case of Wilson's Disease, which had developed three years after an attack of jaundice with hepatomegaly, was seen in a boy of 17. The family history was good, with no suggestion of heredo-familial factors. The clinical picture which the boy presented was typical of the condition.

His blood copper, estimated by Tompsett's method (1934), was found to be 0·30 mgm. per 100 c.c.; above the normal finding of 0·185 to 0·229 mgm. per 100 c.c., according to Tompsett.

Autopsy confirmed the diagnosis. A marked excess of copper, estimated by the sodium diethyl-dithio-carbamate method, was found in the liver (4·6 mgm. per 100 gm.) and the basal ganglia (1·275 mgm. per 100 gm.), and to a lesser extent in the cortex (0·781 mgm. per 100 gm.).

Liver Cirrhosis and the Basal Ganglia.—There can be little doubt that hereditary factors were of the greatest importance in Case 1, although I have not seen a reference to hereditary transmission in the literature.

In the second case, lenticular disease appeared three years after an illness in which the liver became enlarged, in the absence of a family history of neurological disorder.

Wilson argued that the liver cirrhosis preceded the lenticular degeneration, because it is always a constant feature and often is found before lenticular symptoms develop. The researches of Alexander (1942) into the pathology of carbon monoxide poisoning and his demonstration of the existence of a " time-factor," sometimes lasting years before striatal symptoms become apparent, destroys the validity of Wilson's argument.

The occurrence of liver cirrhosis only in " lenticular " families is suggestive evidence in favour of Wilson's view.

Recent pathological studies, however, have shown that lenticular degeneration can develop in cases of liver damage of varying ætiologies.

Thus Alexander (1942) has seen pallidal disease develop clinically in a chronic alcoholic aged 51, with portal cirrhosis. The histological picture in the brain resembled that of Wilson's disease. Waggoner and Malamud (1942) describe 5 cases of acquired liver disorder showing fundamental clinical and pathological similarities in the cerebral manifestations to those found in Wilson's disease. Two of their cases were associated with alcoholism; one had a diffuse gummatous hepatitis, and the remaining two were diabetics with atrophic and cirrhotic livers. The ages of these cases ranged from 44 to 68 years. Stadler (1935) has collected 15 similar cases from the literature, in which neurological signs, frequently of the extra-pyramidal type, and Alzheimer glia cells or degenerative lesions in the basal ganglia, were commonly found.

Nervous symptoms usually appear toward the end of the disease in the acquired liver cirrhoses of domestic animals, and are known as " liver staggers." In Schweinsberg disease of horses, and in Dunsiekte of cattle, nervous symptoms may appear early and in a severe form. They consist of vertigo, gait disorder, straining forward with the forehead pressed against a wall, stupor and lethargy (Hutyra, Marek and Manninger, 1938).

Theiler (1918) describes the additional symptoms of yawning and of laryngeal spasm in Dunsiekte. Kalkus, Tripper and Fuller (1925), investigating enzootic hepatic cirrhosis of horses in the Pacific North-West, found the disease named locally " the walking disease "; for once the beasts commence walking they find it difficult to stop. Postural disturbances are reflected in an unsteady gait and an open mouth.

Dobberstein (1926) describes clinical symptoms in horses suffering from cirrhosis of the liver, presenting a marked similarity to Wilson's disease. Autopsy showed degenerative lesions in the cortex and the caudate nuclei very like those of hepato-lenticular degeneration, including the presence of Alzheimer glia cells. Heidigger (1935) also found lesions in the molecular layers of the brains, and in the caudate

nuclei, of animals suffering from liver cirrhosis consequent upon distomatosis and hydatid infestation.

Thus it seems established, both in man and in domestic animals, that degeneration of the basal ganglia is liable to occur whenever the liver is badly damaged, whatever may be the cause of this damage. Rare in man, the sequence is more commonly seen in domestic animals. Where Wilson's disease is found in a familial form, no doubt the primary inborn defect lies in the liver.

The circumstances under which 14 simultaneous cases of an acute degenerative striatal disease occurred amongst Shantung villagers (Woods and Pendleton, 1925) are more likely related to chronic famine conditions and unsuitable diets than to inborn defects, and seem similar to those factors which cause outbreaks of Dunsiekte and Schweinsberg disease in cattle.

Rôle of Copper.—According to Cunningham (1931) the average copper intake of human beings is five times the requirement. Excess copper is excreted partly in the urine and partly by the liver, copper being a constant constituent of the bile (Judd and Dry, 1935), and the bulk of both clinical and experimental evidence points to the fact that the normal liver can handle large amounts of copper.

Waggoner and Malamud (1942) are of the opinion that whatever difference may exist between the groups of ordinary liver disorders and Wilson's disease ultimately depends on the nature of the underlying liver dysfunction. The function of excreting copper seems to be impaired in some cases of hepatic cirrhosis and not in others; for an inconstant finding is an excess of copper in these livers (Schönheimer and Herkel, 1930), whether the cirrhosis be atrophic or hypertrophic in type (Kleinmann and Klinke, 1930). It is well known that large amounts of copper accumulate in the tissues in Wilson's disease, and as much as fifty times the normal amount has been found in the liver in this condition. In the case reported here an excess was found in the blood during life, and in the liver, cortex and basal ganglia after death.

What effect does an excess of copper have upon the tissues? Like the other heavy metals, copper is a powerful inhibitor of enzymic activity, even in dilute solution. The exceptionally rich blood supply of the basal ganglia affords an indication of the great respiratory demands of these tissues, and they are in fact peculiarly susceptible to damage by inhibitors of enzymic activity, such as cyanide and carbon monoxide. Alexander (1942) discusses the histological appearances of the putaminal lesions in a case of " alcoholic " liver cirrhosis, which so closely resembled those found in Wilson's disease. The type of parenchymal destruction and glia-mesenchymal reaction is essentially that which would be expected in a focal lesion of necrosis due to an interference with the blood supply. He suggests that the obvious oxygen deprivation of the involved tissues, in spite of the absence of vascular occlusions, may be due to lack of substances other than the streaming blood. He cites the possible lack of an activator of oxidative activity of the order of a metabolic catalyst or vitamin.

As copper in a strength as dilute as 0·636 mgm. per 100 c.c. inhibits glycolysis in muscle (Lipmann, 1934), the concentration found in the basal ganglia of the case reported here (1·275 mgm. per 100 gm.) may well be sufficient to impede respiration by enzymic inhibition, and ultimately cause necrosis. A more practical possibility is that a raised blood copper may prove to be of diagnostic and prognostic importance.

SUMMARY

1. An hereditary illness, having the clinical features of Wilson's disease, is described.

2. An increased blood copper content has been found in a case of Wilson's disease. The observation may prove to be of diagnostic and prognostic value.

3. Inability to excrete copper may be the liver dysfunction responsible for the production of lenticular degeneration.

I am very grateful to Dr Elizabeth Gilchrist of the Royal Infirmary and Dr Henry Tod, of the Royal Edinburgh Hospital, for their determinations of copper in tissues and blood. I wish to thank Professor D. M. Lyon and Professor D. K. Henderson for their stimulating encouragement, and Dr R. B. McMillan, Medical Superintendent of the Western General Hospital, for his permission to publish Case 1.

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OBITUARY

WILLIAM THOMAS RITCHIE

O.B.E., M.D., LL.D., F.R.C.P.Ed., F.R.S.Ed.

THE very sudden death of Emeritus-Professor William Thomas Ritchie on 7th February 1945, at his house at Barnshot Road, Colinton, Edinburgh, must have come as a shock to his many friends, for up to the last he was actively engaged in a variety of professional capacities.

Born in Edinburgh on 5th November 1873, the only son of Robert Brown Ritchie, of 31 Great King Street, William Ritchie was educated at the Edinburgh Academy and the University of Edinburgh, where he graduated M.B., C.M. in 1896. Those of us who knew him intimately recognised, even in those early days, that he had qualities and characteristics which were bound to bring him to the front in the years to come.

After serving as house-physician to Dr Affleck in the Royal Infirmary, and as house-surgeon to Mr Pringle in Glasgow, Ritchie spent some months in Vienna. Upon his return to Edinburgh he devoted much of his time for the next year or two to bacteriological research in the laboratory of the Royal College of Physicians. Elected a Member of the Royal College of Physicians in 1900, a Fellow of the College in 1903 and a Fellow of the Royal Society of Edinburgh in 1905, he was attached as a clinical tutor to Dr George A. Gibson's wards in the Royal Infirmary from 1900 to 1905, as pathologist to Leith Hospital from 1902 to 1906, and as assistant pathologist to the Royal Infirmary from 1906 to 1910. In 1906 he collaborated as co-author with Dr Graham Brown in revising the enlarged fifth edition of the latter's book on Medical Diagnosis. Appointed an Assistant Physician to the Royal Infirmary in 1911 and Physician to the Deaconess Hospital in 1913, he produced his admirable monograph on Auricular Flutter in the following year.

At the outbreak of the First Great War in 1914, Ritchie was on the Staff of the 2nd Scottish Hospital, Craigleith, as a Captain R.A.M.C. (T.). But he was almost immediately posted as Medical Officer to the 1/3rd Scottish Horse and served with this Unit in Gallipoli. Later, as an acting major, he was in charge of the Medical Division of the 27th General Hospital in Egypt, and occupied this post until the cessation of hostilities when he was awarded the O.B.E.

Upon demobilisation Ritchie returned to Edinburgh. The writer's impression is that at this period of his career he would have liked nothing so much as a post with a laboratory and clinical facilities under his care which would have enabled him to devote his whole time to research and teaching. In 1922 he was appointed a full physician to the Royal Infirmary and soon after Principal Medical Officer to the Edinburgh Insurance Company. At various times he acted as external examiner in Medicine in the Universities of St Andrews, Durham and Aberdeen, and for years he was busily engaged in consulting practice.

Ritchie was elected to the Professorship of Medicine, an office for which he had had an ideal training, in 1928, and during his tenure devoted himself wholeheartedly to the interests of the Chair. The essential duties of the

Photo by *Swan Watson, Edinburgh*

WILLIAM THOMAS RITCHIE

Professor of Medicine, in addition to his hospital work and teaching, had hitherto been to deliver a daily systematic lecture during the Autumn and Spring terms and, with the assistance of one external examiner, to conduct the written and oral examinations in Medicine. But at the time of Ritchie's appointment the teaching arrangements were remodelled by the University. A series of co-ordinated lectures upon Pathology, Bacteriology, Medicine, Surgery, Therapeutics and Pharmacology, spread evenly throughout the year, now replaced the course of a hundred consecutive lectures previously delivered upon these subjects. Ritchie was personally responsible for further notable changes which redound to his credit. He arranged that additional external examiners should take part in the final examinations in Medicine; he instituted meetings in the Royal Infirmary related to his systematic lectures; he arranged, in conjunction with the Professor of Pathology, for a series of associated demonstrations, which were much appreciated by the students, and he established a Department of Medicine in the University.

As President of the Royal College of Physicians from 1935 to 1937, the dignity and courtesy with which Ritchie presided met with universal approbation. He retired from the University Chair in 1937, but soon after the outbreak of the present war he took over temporary charge of the wards of a colleague in the Royal Infirmary who was on military service. Up to the time of his death he was acting as Physician to the Emergency Medical Hospital at Bangour.

The field of Medicine is nowadays so extensive that the physician who would make advances and acquire a reputation must of necessity concentrate upon some particular department. It is not surprising that Ritchie, with his interest in research, should have selected Cardiology as the specialty of his choice, for in the opening years of the twentieth century the study of the heart and circulation was being revolutionised by the new methods and researches of James Mackenzie, Einthoven and Wenckebach. Ritchie had the good fortune also to be associated at this time as clinical tutor with George A. Gibson, and thanks to Gibson's influence, and the generosity of an anonymous donor, a small room was set apart in the Royal Infirmary as a clinical laboratory and a string galvanometer installed of which he made full use. Among his contributions to the literature, one of his early papers, written in collaboration with George Gibson and entitled "An Historic Instance of the Adams Stokes Syndrome," is of particular interest. It is a curious coincidence, is it not, that James Mackenzie, Gairdner, Gibson and Ritchie all died from cardiac disease? The monograph on Auricular Flutter—a disorder described clinically by Ritchie and Jolly in 1911 although originally observed by Macwilliam on stimulation of the mammalian heart by weak Faradic currents many years previously—was published in May 1914. "The Response of the Heart in Health and Disease" was the title of his Gibson Memorial Lecture in 1922. He collaborated as co-author in 1935 with John Cowan in the third edition of the latter's well-known book on Diseases of the Heart. In 1939 he delivered the St Cyres Lecture. Ritchie's writings are all well worth reading as contributions to knowledge; they are characterised too by the good, clear, virile English with which he expressed himself. His references were checked with scrupulous care.

One had to know Ritchie, and he was not an easy man to really know, to appreciate to the full his sterling qualities. A rather formal manner obscured a most kindly and approachable personality. He rarely expressed

himself in enthusiastic terms and he was not a gallery man. After committing himself to an opinion he seldom modified it; he was not by temperament a compromiser. But if when serving on a committee he sided with the minority, as was not uncommonly the case, his colleagues respected his opinion for they recognised that he always said what he believed was for the common good and that his views were never influenced by his personal interests. As an examiner he did not pander to popularity; he looked for a high standard but was always anxious to be scrupulously fair. Very thorough as a clinician and indeed in everything he did, he expected thoroughness in others. Incompetency, slackness, self-seeking, pseudo-scientific medicine and chicanery aroused his ire, which he expressed in no uncertain terms. Ritchie set himself high ideals and he lived up to them. The conferment upon him of the honorary degree of LL.D. only last summer was a fitting recognition of the good services of a gentleman to his Alma Mater, to Medicine and to his Profession in the best tradition of the Edinburgh School.

E. B.

NOTES

Triple Qualification Board.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations and were granted the diploma of L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG. :—William Caldow Adam, John Henry Beckford, Matthew Gillespie Blackwood, George Warren Blueglass, William Joseph Connelly, Albert Wallace Craig, Bernard Cutler, Andrew Alexander Donaldson, Leicester Perry Eaton, James Fegan, Thomas Maxwell Glaister, Sidney Morris Harris, Cacilia Margareth Hofer, Jean Hughes, Joseph Douglas Jack, Solomon Jesner, Helen Teresa Kilpatrick, Stuart John MacKinnon, Archibald McKirdy, William Donald MacLennan, Alexander Bruce Marshall, Albert Leonard Nowell, Dalziel Peebles, David Roy Lavington Peill, Francis Callow Place, William Roberts, Joseph Rubin, Douglas Gavin Scott, Ali Ali El Serougi, Benjamin Meyer Steen.

Royal College of Physicians of Edinburgh.

A QUARTERLY Meeting of the College was held on Tuesday, 6th February, the President, Dr A. Fergus Hewat, in the Chair. Dr Wm. Francis Theodore Haultain, O.B.E., M.C. (Edinburgh), was introduced and took his seat as a Fellow of the College. Dr David Randolph Maitland (Cupar, Fife) and Dr Ian Douglas-Wilson (Harrogate, Yorks) were elected Fellows of the College.

University of Edinburgh.

AT a Graduation Ceremonial held on Saturday, 20th January 1945, the following degrees were conferred :—

The Degree of Doctor of Medicine :—Maurice Edwin Spencer Harrison, England, M.B., CH.B., 1936 (*In absentiâ*); Alan Stewart Johnstone, England, M.B., CH.B. (*with Honours*), 1927; Iain Fraser MacKenzie, Scotland, M.B., CH.B., 1932; Esmé Gordon Lennox Mark, B.SC., Scotland, M.B., CH.B., 1935 (*In absentiâ*); John Mackenzie Matheson, Scotland, M.B., CH.B., 1936 (Lt.-Col., R.A.M.C.) (*In absentiâ*); Joseph Buford Pennybacker, B.A. (Tennessee), M.A. (Oxon) U.S.A., M.B., CH.B. (*with Honours*), 1930 (*In absentiâ*); Henry George Triay, Gibraltar, M.B., CH.B., 1922 (*In absentiâ*).

The Degree of Doctor of Science :—James Norman Davidson, B.SC., M.D.

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The Polish School of Medicine at Edinburgh—The Degrees of Bachelor of Medicine and Bachelor of Surgery:—Stanislaw Kazimierz Ganczakowski, Władysław Juchnowicz, Wiktor Jurewicz, Stefan Okolski.

NEW BOOKS

The Sick African. A Clinical Study. By M. GELFAND, M.B., CH.B., M.R.C.P., D.M.R. Cape Town: The Stewart Printing Co. Ltd. 1944. Price 25s. net.

"This book does not pretend to be a textbook, but rather a guide to those working amongst natives." As such, it should be studied on the voyage out by all those taking up practice in Africa for the first time. Further, the practitioner in out-stations, probably separated from larger books of reference, will find much to help him within its pages. This book is of the African, his peculiarities and difficulties as a patient, the diseases to which he is subject, the influence of environment on his health and the manner in which his reactions differ from those of European patients. The author lays timely stress on the fact that natives of tropical countries do not suffer exclusively from diseases peculiar to tropical climates and gives a brief description of many diseases of world-wide distribution. Criticism might be levelled at the width of the subject embraced within the confines of a comparatively small volume, but the author has a definite object in view—that is, to provide a portable book of reference not only for medical men, but also for missionaries and native medical orderlies. It is interesting to note that the author regards rheumatic fever and carditis as by no means uncommon, but chorea as exceedingly rare. This bears out experience in India, and his observations may help to disturb the contention, somewhat obstinately held, that rheumatic fever does not occur among the inhabitants of tropical climates. The book includes a large number of admirably reproduced and instructive illustrations.

X-ray Examination of the Stomach. By FREDERIC E. TEMPLETON. Pp. iv+516, with 297 illustrations. Chicago, Illinois: The University of Chicago Press. 1944.

In this new book on the radiological examination of the pharynx, œsophagus, stomach, duodenum and pancreas special attention is paid to the technique of examination. Hitherto in America it has been customary to rely mainly on fluoroscopic examination, but the author points out that the evidence obtainable by this means is in many cases insufficient to permit of an exact diagnosis. If the finer points concerned with differential diagnosis are to be obtained, it is essential to take a series of radiographs. Each radiograph is taken under screen control and the position so selected as to provide the best possible view of the lesion.

A considerable section is devoted to the study of the normal, and the special means of investigation employed by the author has enabled him to present much valuable information concerning the variations in the normal appearances of these organs. The detailed study has contributed much to the knowledge of disease in its early stages.

The appearances of the various lesions are well described and the illustrations are of good quality. There is a useful chapter at the end of the book on differential diagnosis. A limited but good bibliography is provided.

The book can be very strongly recommended, and will be found of considerable value even to the experienced radiologist.

A Bibliography of Aviation Medicine—Supplement. By P. M. HOFF, E. C. HOFF and J. F. FULTON. Pp. xiv+109. Springfield: Charles C. Thomas. 1944. Price $2.50.

During the two years that have elapsed since the appearance of the parent volume, literature on the medical aspects of aviation has expanded at a phenomenal rate. This supplementary bibliography has been drawn up to make immediately available all information on this important subject. Over 2000 new entries have been listed and this work should prove of the greatest service to those interested in this field of medicine.

The Mode of Action of Sulfonamides. By RICHARD J. HENRY, M.D. Publication of Josiah Macy Jr. Foundation, 1944.

This book contains a comprehensive discussion of the great mass of biochemical and biophysical work that has been done in the search for the satisfactory explanation of the mode of action of sulphonamides on bacteria. Much of the discussion centres round the theory advanced in 1940 by Woods and Fildes who discovered that the sulphanilamide (S.A.) did not prevent bacterial growth in the presence of an excess of para-amino benzoic acid (P.A.B.A.) and suggested that S.A. stopped growth by competing with the P.A.B.A. for chemical groups in the bacteria, so that the same chemical reaction, involving P.A.B.A. and essential for growth, did not occur. This theory has been widely accepted, but the evidence on which it rests is not as good as is sometimes assumed.

Some bacteria cannot grow unless P.A.B.A. is present in the medium. In this case it is obviously an essential metabolite. Most bacteria grow well in media containing no P.A.B.A. The theory assumes that P.A.B.A. is still an essential metabolite but that the organisms synthesize it for themselves; there is, however, no satisfactory direct evidence that this is so.

This gap in the evidence may well be filled in time, but there is other evidence which seems to show that the original theory may have to be discarded because it does not account for all the facts. For example, it has been found that P.A.B.A. antagonises the inhibitory action of S.A. on various simple enzyme reactions in which P.A.B.A. probably plays no part. Further, a number of other substances, such as methionine, have been found to antagonise S.A., though it is unlikely from

a chemical point of view that they are competing for the same groups as P.A.B.A. It may well be that these substances act quite differently from P.A.B.A., but the fact that they do act as antagonists to S.A. stimulates the search for a theory which will explain the actions of all antagonists.

A large amount of interesting work has been done in this field and in the search for an explanation of the different actions of the different sulphonamides. The book contains a detailed review of this work and will be very valuable for those doing research in this field. It does not deal with the practical problems of the use of sulphonamides in therapeutics.

Modern Treatment Year Book 1944. Edited by CECIL P. G. WAKELEY, C.B., D.SC., F.R.C.S. Pp. viii+211, with 15 illustrations and 17 plates. London: Medical Press and Circular. 1944. Price 15s.

This annual is now the tenth in the series. Like its predecessors it consists of a number of articles on modern diagnostic and therapeutic methods, bringing the subjects up to date. Some forty eminent writers contribute papers on various fields of medical endeavour. Many of the subjects reviewed have been brought into prominence by war conditions, so the book should be of special interest to medical men in the Services.

A Guide for the Tuberculous Patient. By G. S. ERWIN, M.D. Pp. viii+115. London: William Heinemann, Medical Books, Ltd. 1944. Price 3s. 6d. net.

This book has been written to provide the tuberculous patient with some knowledge of the disease from which he suffers and so afford a basis on which he may apply general principles to his own particular case. In no other disease is the intelligent co-operation of the patient more necessary, both during and after the period of hospital and sanatorium treatment. The book is clearly written and should be of great value to the "tuberculous" patient.

Aids to Clinical Pathology. By DAVID HALER, M.B., B.S., D.C.P. Pp. viii+358. London: Baillière, Tindall & Cox. 1944. Price 6s. net.

The author has intended this small textbook to be used by students and post-graduates interested in pathology and laboratory work. It is a continuation of the old "Aids to Pathological Technique" and the "Aids to Practical Pathology." Alternative methods are given for most of the estimations and these are described briefly and clearly. This book should prove of value to those engaged in practical pathology, laboratory and post-mortem work.

Studies on Immunisation. Second Series. By Sir ALMROTH E. WRIGHT. Pp. 256, with 17 figures and one coloured plate. London: William Heinemann, Medical Books, Ltd. Price 25s. net.

This is the fourth volume of the collected "Researches from the Inoculation Department of the St Mary's Hospital, London."

The present volume contains reprints of nine papers published between 1910 and 1942, with appendices containing four other reprinted papers or extracts dating from 1904, one of them by R. M. Fry.

The debt due by medicine to the distinguished author, particularly in regard to his pioneer work in the use of vaccines and in his perfection of a particular form of experimental laboratory technique, is well known. Many bacteriologists of repute were pupils of Wright, and their later work often still shows the results of early contact with his mind and methods. This influence can be observed, for example, in the laboratory methods used by Fleming in some of his studies on penicillin.

These papers, like most of those written by Wright, are difficult to read, being set forth in the style peculiar to himself, with many descriptive terms coined from the Greek.

Most of them were written before organisms had been divided into their numerous serological types, and before the days of the resolving of bacteria into their different antigenic components. In studying them, therefore, the reader is constantly testing in his mind the arguments and conclusions of the author in the light of what is now known, and inevitably he finds things which would require re-examination or re-statement if the papers were rewritten at the present time.

But even to-day much can be learned from careful reading of these reprints.

The volume is handsomely produced.

Notable Names in Medicine and Surgery. By HAMILTON BAILEY, F.R.C.S., and W. J. BISHOP, F.L.A. Pp. viii+202, with 142 illustrations. London: H. K. Lewis & Co. Ltd. 1944. Price 15s. net.

The authors point out that certain proper names are in daily use in medical practice yet few know anything of the famous men who bore them. Gooch's splint, Dover's Powder, Dupuytren's contracture, the fissure of Rolando are examples.

The book contains a series of vignettes of about eighty notable men whose names have been commemorated in this way in various departments of medicine. Each biographical note is illustrated by a portrait and there are many pictures of old hospitals, instruments and so forth.

This collection of names should give an added interest to the daily work of the doctor.

NEW EDITIONS

Recent Advances in Endocrinology. By A. T. CAMERON, M.A., D.SC. Fifth Edition. Pp. vii+415, with 70 illustrations and 3 plates. London: J. & A. Churchill. 1944. Price 18s.

In spite of the distractions caused by war, there has apparently been no diminution in the number of papers published on endocrine subjects and some outstanding advances have been made since the last edition of this book appeared in 1940.

The present edition has been almost completely re-written so as to give more attention to the clinical aspects of the subject. In its present form this book should have a very wide appeal.

Pharmacology. By J. H. GADDUM, SC.D., M.R.C.S., L.R.C.P. Second Edition. Pp. xvi+260, with 75 figures. London: Oxford University Press. 1944. Price 21s. net.

We are glad to be able to welcome the second edition of Professor Gaddum's textbook on pharmacology which has been improved in various ways and brought up to date. The book is primarily intended for medical students and it claims to include all information sought by examiners. Most of the information given is worth remembering, but some details have been included only for reference. It ought also to be of interest to the medical man who wishes to keep up his knowledge of the foundations of treatment.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN. Third Edition. Pp. 516, with 103 illustrations and 4 colour plates. London: Henry Kimpton. 1944. Price 30s. net.

In the third edition of this compact little book the author has introduced new material from the war medical literature, notably on immersion foot, "effort syndrome," and the examination of candidates for military and flying service. There are valuable sections on the study of patients suspected of having heart disease and on the techniques of accessory methods of examination, and a well-illustrated, authoritative chapter on electrocardiography. In the chapters devoted to the various ætiological and anatomical varieties of cardiac disease emphasis is laid on the disturbances

of the normal physiological mechanism. The paragraphs on morbid anatomy have been rigidly condensed, but those describing the clinical pictures and differential diagnosis are detailed and clear. There is a most useful chapter on peripheral vascular diseases. The diagrams, drawings and photographs are carefully selected and well reproduced.

This book can be recommended to student and practitioner alike.

A Manual of Diseases of the Eye. By C. H. MAY, M.D., and CLAUD WORTH. Revised by M. L. HINE, M.D., F.R.C.S. Ninth Edition. Pp. viii+538, with 371 figures, many in colour. London: Baillière, Tindall & Cox. 1944. Price 16s.

This well-known textbook needs little recommendation to the profession. The present edition continues the tradition of its predecessors, but certain sections have been altered in the light of recent advances. Changes in therapy have been important, vitamins, sulphonamides and penicillin offering better facilities to the practitioner. The book is excellently produced and beautifully illustrated. It should continue to be the standard undergraduate textbook on the subject.

BOOKS RECEIVED

ARMSTRONG, J. R., M.D., M.CH., F.R.C.S. Bone-grafting in the Treatment of Fractures . . . . . (*E. & S. Livingstone, Ltd., Edinburgh*) 25s. net.

BORRADAILE, L. A., SC.D. A Manual of Elementary Zoology. Eleventh Edition . . . . . (*Humphrey Milford, Oxford University Press, London*) 24s. net.

COWDRY, E. V. A Textbook of Histology. Third Edition. (*Henry Kimpton, London*) 35s. net.

CURRIE, J. R., M.A., M.D., LL.D., D.P.H., F.R.C.P., and A. G. MEARNS, B.SC., M.D., B.SC., D.P.H., F.R.S. Hygiene. Second Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 21s. net.

DAWSON, W. S., M.A., M.D., F.R.C.P., F.R.A.C.P., D.P.M. Aids to Psychiatry. Fifth Edition. . . . . (*Baillière, Tindall & Cox, London*) 6s. net.

JAMIESON, E. B., M.D. A Companion to Manuals of Practical Anatomy. Sixth Edition. . . . . (*Humphrey Milford, Oxford University Press, London*) 16s. net.

KEERS, R. Y., M.D., F.R.F.P.S., and B. G. RIGDEN, M.R.C.S., L.R.C.P. Pulmonary Tuberculosis . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 17s. 6d. net.

MACDONALD, DAVID MITCHELL, M.D., D.P.H., F.R.C.P.E. The Students' Pocket Prescriber and Guide to Prescription Writing. Twelfth Edition. (*E. & S. Livingstone Ltd., Edinburgh*)

MACKIE, T. J., C.B.E., M.D., D.P.H., and J. E. MCCARTNEY, M.D., D.SC. Hand-book of Practical Bacteriology. Seventh Edition. (*E. & S. Livingstone, Edinburgh*) 4s. net.

OAKES, LOIS, S.R.N., D.N. Illustrations of Bandaging and First Aid. Third Edition. . . . . (*E. & S. Livingstone, Edinburgh*) 17s. 6d.

PHILLIPS, RALPH, M.S., M.B., F.R.C.S., D.M.B.E., and G. S. INNES, B.SC., A.M.I.E.E. Supervoltage X-Ray Therapy. A Report for the years 1937-1942 on the Mozelle Sassoon Supervoltage X-Ray Therapy Department, St Bartholo-mew's Hospital . . . . . (*H. K. Lewis & Co., Ltd., London*) 6s. net.

SCHERF, DAVID, M.D., and LINN J. BOYD, M.D., F.A.C.P. Clinical Electro-cardiography. Second Revised Edition. (*William Heinemann, Medical Books, Ltd., London*) 16s. net.

SELLING, LOWELL S., SC.M., M.D., PH.D., DR.PH. Synopsis of Neuropsychiatry. (*Henry Kimpton, London*) 25s. net.

SPAETH, EDMUND B., M.D. The Principles and Practice of Ophthalmic Surgery. Third Edition . . . . . (*Henry Kimpton, London*) 25s. net.

TIDY, SIR HENRY LETHEBY, K.B.E., M.A., M.D., B.CH., F.R.C.P. A Synopsis of Medicine. Eighth Edition, Revised and Enlarged. (*John Wright & Sons Ltd., Bristol*) 50s. net.

WIGGERS, CARL J., M.D., D.SC., F.A.C.P. Physiology in Health and Disease. Fourth Edition . . . . . (*Henry Kimpton, London*) 30s. net.

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Edinburgh Medical Journal

March-April 1945

THE THEORY OF ANAPHYLAXIS AND THE THERAPEUTIC POSSIBILITIES IN RHEUMATISM

By WALTER M. LEVINTHAL, M.D., F.R.S.Ed.

Bacteriologist, Royal College of Physicians' Laboratory, Edinburgh

IN an article on the " Ætiology of Rheumatism " I have summed up my views in the following conclusion :—

Rheumatism, acute and chronic, is an anaphylactic disease due to continual antigen-antibody reactions in the cells of the mesodermal system. The antigen in most cases is derived from the sites of subacute or chronic bacterial infection. The antibody is distributed in the faulty way characteristic of sensitisation, viz. mainly within the cells and deficient in the circulation. This anaphylactic distribution of the antibody is due to the quantitatively insufficient response of the reticulo-endothelial system to immunising stimuli which leads to a state of imperfect immunity. The debility, constitutional or temporary, of the antibody-producing organ is the basic cause of rheumatism.

I propose in the present paper to discuss, in the light of the quoted conception, the rationale of rheumatism therapy.

There are two different ways of approach for attacking the anaphylactic tissue reaction : the attempt to render it harmless, and the attempt to abolish it. The first would aim at a " detoxication " of the anaphylactic reaction, the second at its prevention.

I. THE " DETOXICATION " OF THE ANAPHYLACTIC REACTION

Why is the clash between an antigen and the corresponding antibody, their physico-chemical interaction, if taking place in or on tissue cells, a harmful event for the tissues concerned ? What is the mechanism in the irritation of the cells with the dramatic effect of collapse or death in the case of anaphylactic shock or with the insidious development of anaphylactic inflammation ? In 1919 it was observed by Dale and Laidlaw that apparently the same set of phenomena, general and local, can be produced by histamine. If injected intravenously into a normal guinea-pig a shock occurs simulating the effect of an intravenous injection of protein into a specifically sensitised animal. If tested on isolated organs such as intestines or uterus a

contraction similar to the reaction in the Dale or Massini experiment is registered. Moreover, in anaphylactic reaction the appearance of an H-substance (histamine-like substance) can be directly observed. So Dale and Laidlaw assumed that the specific reaction between antigen and antibody in cells releases histamine, a natural cell constituent, from these cells in great amount and so suddenly that the toxic effect of the substance becomes manifest. The anaphylactic reaction was interpreted as a histamine reaction. This far-reaching identification is no longer tenable, but it appears that histamine or a histamine-like substance plays an important part in anaphylactic phenomena. If the liberation of histamine from anaphylactically reacting cells could be inhibited or the liberated substance be destroyed at once, a serious tissue damage might be prevented.

Anti-histamine Effect of Histaminase.—In 1930 a histamine-destroying enzyme was discovered by Best and McHenry in various tissues, especially kidney and intestine, and later this histaminase was commercially produced from the small intestine of the pig under the name of Torantil or T 360 (Bayer, Germany, and Winthrop, Toronto). The first clinical trials with the new preparation in Germany (since 1934) turned out to be rather disappointing or at least ambiguous (*e.g.* Adelsberger, 1937), but soon quite a number of striking experimental results and clinical successes were reported in America. Foshay and Hagebusch (1939) claimed prompt relief in the treatment of serum sickness and, if it were prophylactically given, prevention in all cases. Cures in allergic dermatoses such as urticaria were reported (*e.g.* Alexander and Elliot, 1940, Laymon and Cumming, 1939, Goldberg, 1940), and were denied or sceptically viewed by others. Similar contradictory results were obtained in cases of hay fever and asthma by different observers.

Laboratory experiments were published (Haag and Lutz, 1939, and shortly afterwards Karady and Browne) which seemed to give a sound basis for the clinical use of histaminase. Although sensitised guinea-pigs could not be completely protected by a histaminase injection given shortly before the anaphylactic test dose, the severity of the shock was greatly reduced and a number of animals were saved from the fatal effect. Thus a fierce campaign for and against the therapeutic use of the drug in anaphylactic conditions went on, until Best and McHenry themselves in a "Note on Histaminase" (1940) exploded the whole performance with the categoric statement that "their investigations over a period of ten years have failed to show that intravenous or intramuscular administration of histaminase (preparations at least four times as potent as any commercially available) has any effect on histamine present in the body or on that given by injection." The claims of success after oral administration seem even more phantastic as the drug is rapidly destroyed by pepsin and trypsin, and "could hardly survive the action of the proteolytic enzymes." The protection of guinea-pigs against anaphylactic and histamine

shock was attempted by Best and McHenry long before Karady and Browne "with completely negative results," and after the publication by Karady and Browne the experiment was repeated with the same failure. Best and McHenry refute any responsibility for the clinical use of the enzyme for which there is no physiological basis. A similar verdict was arrived at in the " Preliminary Report on Histaminase " by the American Council on Pharmacy and Chemistry in 1940, where a good informative review is given. " In the opinion of the Council the use of histaminase in the treatment of allergic states, although perhaps ingenious and suggestive, has no well-established scientific clinical basis."

And yet, a very interesting publication by Scholer (1933) on " Comparative investigations on local anaphylaxis of various organs " may have a direct bearing on the part played by a histaminase in the anaphylactic phenomenon. Scholer found that, while in thoroughly sensitised rabbits the re-injection of the antigen into the wall of the stomach produces the typical anaphylactic reaction with œdema and infiltration, stasis in the capillaries, even necrosis, the intestines and mesentery remain refractory after subserous, intra- and submucous injection. The author shows that this non-reactivity is not due to a " lack of readiness for inflammation " of the intestinal tissue nor to the absence of the antibody; the passive anaphylactic experiment (injection of antibody, followed by the injection of the corresponding antigen) exhibits the same non-reactivity. Scholer has no explanation to offer for this refractoriness of a tissue, susceptible to inflammatory irritation, in the local antigen-antibody reaction, demonstrated for the first time by him. It seems, however, a sound assumption to attribute the absence of an anaphylactic manifestation in the intestinal wall to the abundance of histaminase in that tissue, in accordance with the view of Best and McHenry that the natural presence of the enzyme in various tissues " may constitute one of several defence mechanisms for the inactivation of histamine."

Anti-histamine Effect of Antagonistic Substances.—A similar series of studies on anaphylaxis and histamine, but with a very different type of anti-histaminics, was inaugurated in 1937. Bovet and Staub embarked on a systematic search for substances antagonistic to histamine. They tested a number of preparations synthetised in the laboratory of Fourneau, and found amongst certain amines of phenol ethers some which possess a definite anti-histamine effect. Mlle. Staub in a long paper (1939), with many chemical details, covered the whole field investigated so far; and Rosenthal and Brown (1940) confirmed the results of the French authors. The main attention of the investigators was devoted to the preparation 929 F, a thymoxyethyldiethylamine, possibly identical with the Japanese therapeutic drug Tostramine, although the latter is much better tolerated by man than the very toxic French product.

The anti-histamine effect of thymoxyethyldiethylamine is manifest

on the smooth muscles (intestine, uterus, etc.), but absent against the vascular phenomena of the skin (Lewis' three-zone reaction). The drug protects guinea-pigs against fatal histamine shock, but the mode of its action remains obscure. It is certain, however, that histamine is not destroyed nor is the enzymic effect of histaminase on histamine increased. The part of these studies most relevant to our subject is the investigation of the anaphylactic shock *in vivo*, and of the anaphylactic reactions on isolated organs of sensitised animals. The contraction of the sensitised intestine and uterus is abolished if the organ is treated with the drug shortly before the addition of the antigen. Sensitised guinea-pigs are partially protected and often saved from fatal shock if the drug is injected shortly before the application of the antigen (an interval of 24 hours is without effect). This protection, however, is mainly confined to the spastic reaction of the bronchi. Malaise and severe prostration for one or several hours remain unchecked. So it seems that the anti-histaminic drug acts only on one component of the complex anaphylactic phenomenon, confirming the view that histamine plays but a partial rôle in anaphylaxis.

Anti-histamine Effect by Prevention of Histamine Liberation.— The same partial effect was noticed by Hochwald (1935 and 1936) in very important investigations on the rôle of reducing substances, such as ascorbic acid, glutathion, cysteine and certain thiosulphates in anaphylaxis. Jusatz, Bersin and Koester (1935) had shown that immunisation of rabbits uses up ascorbic acid and glutathion, and may even lead to a complete exhaustion of these substances in their principal depôts, the blood and the suprarenals. If the animals during immunisation are kept on a diet poor in or free from vitamin C, the immunisation response, the formation of antibodies, is impeded. On the other hand, this depletion of the reducing substances can be prevented, and the production of antibodies is increased by the administration of ascorbic acid during immunisation. Hochwald (1935, 1936) studied the effect of vitamin C on the anaphylactic shock of guinea-pigs and found the following interesting data: a great number of the animals can be saved from fatal shock if large amounts of ascorbic acid are given before the shock-releasing injection of the antigen; this protective action of the vitamin lasts only up to two hours and has nothing to do with its storage in liver and suprarenal cortex, which reaches its climax only 4 to 20 hours after injection. The saved animals become anti-anaphylactic or desensitised for about a fortnight, which proves that the antigen-antibody reaction has taken place. The anti-anaphylactic effect of the vitamin is, therefore, not due to blockade in the reticulo-endothelial system.

On the other hand, ascorbic acid is without effect on shock by histamine. Thus, Hochwald is led to the conclusion that the vitamin acts in the cells between the antigen-antibody reaction and the subsequent liberation of histamine. It is only the histamine component of the anaphylactic complex that is abolished.

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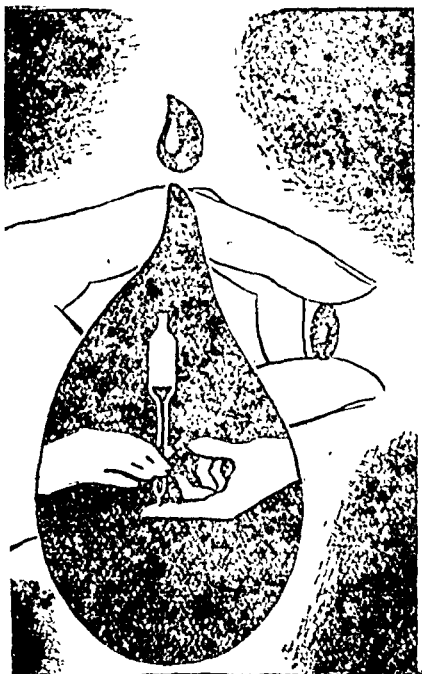

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On these observations the author bases this illuminating hypothesis. The anaphylactic reaction in the cells proceeds in four stages: (1) antigen-antibody reaction, leading to (2) an increased consumption of reducing cell substances, such as ascorbic acid, glutathion, cysteine, magnesium thiosulphate and an upset of the cell metabolism, leading to (3) liberation of histamine, which (4) releases the shock.

If, therefore, one of these reducing substances is abundantly available in the cells during the interaction between antigen and antibody, the disturbance of the intracellular equilibrium and the subsequent liberation of histamine is completely or to a great extent prevented. In accordance with his experimental results and conclusions, Hochwald obtained clinical successes with vitamin C in the treatment of hay fever, asthma and lobar pneumonia.

Hochwald's experiments were confirmed by Giraud, Ratsimamanga and Rabinowicz (1936). His hypothetical interpretation found convincing support in a beautiful *in vitro* experiment by Ungar, Parrot and Levillain (1937). Ungar and Parrot had previously (1936) shown that a fragment of certain organs (lung, kidney, intestine) of a sensitised guinea-pig brought together with the antigen used for the sensitisation liberates a substance indistinguishable from histamine. Now the authors studied with the same experimental arrangement the effect of ascorbic acid, accepting Hochwald's idea as a working hypothesis.

Guinea-pigs were sensitised with horse serum and in due course killed and bled. One of the organs mentioned before was minced and divided into three lots of equal weight.

> To (*a*) were added 4 c.c. of horse serum and 1 c.c. of Tyrode; to (*b*) first 1 c.c. of ascorbic acid solution (final concentration 1 in 10,000), then after 15 to 20 min. 4 c.c. of horse serum; to (*c*) first 4 c.c. of horse serum, then after some minutes 1 c.c. of the ascorbic acid solution.

Controls were set up with the organs of normal animals. Ten minutes later 1 c.c. of the mixtures were tested for the presence of histamine on normal guinea-pig intestines suspended in a Tyrode bath, aerated at 37° C.

> Results: (*a*) and (*c*) strong contraction, histamine present; (*b*) no contraction, histamine absent.

Conclusion: ascorbic acid counteracts the histamine effect of the anaphylactic, *i.e.* the antigen-antibody reaction, but it does not act antagonistically to histamine (shown by the result of (*c*)). Only if added previous to the contact between the sensitised (antibody-containing) tissues and the antigen (horse serum), is no histamine detectable (*b*). Therefore, as Hochwald has assumed, ascorbic acid hinders the liberation of histamine during the antigen-antibody contact in the cells.

It seems relevant to recall a clinical observation recently made by Glazebrook and Scott Thomson (1942). These authors, obviously

unaware of Hochwald's hypothesis, studied the "relationship of vitamin C to resistance" in a large institution with 1500 adolescents who during the preceding session had suffered a severe epidemic of streptococcal tonsillitis. The diet of the youths was considerably deficient in vitamin C as shown by the "surprisingly" large amount (4000 mg.) of ascorbic acid required to achieve tissue saturation. Ascorbic acid in large doses was given to a test group of 335 boys over a period of several months, and the incidence of infectious diseases in this treated group was compared with the corresponding occurrence in the remaining group of 1100 boys (control group). As was to be expected, no difference was observed in the incidence of common cold and tonsillitis, but the duration of this latter disease in the control group (16·7 days) was much longer than in the vitamin C group (10·1 days). This difference would illustrate the stimulating effect of ascorbic acid on immunisation, found by Jusatz, Bersin and Koester in their rabbit tests. However, "the most marked effect of the vitamin C was to reduce the incidence of two severe illnesses." There were seventeen cases of pneumonia (now widely recognised as an anaphylactic condition) and sixteen cases of rheumatic fever, eleven primary, five recurrences, in the control group, and no cases of either disease in the vitamin C treated group. This striking difference appears to support Hochwald's hypothesis.

It should be kept in mind that ascorbic acid is only one of those reducing cell substances used up by the intracellular antigen-antibody reaction. Indeed, magnesium salts have been found to protect sensitised guinea-pigs against anaphylactic shock (Lumière and Malespine, 1929), and have been given with beneficial effect in anaphylactic diseases, *e.g.* asthma (Keller). A glutathion preparation called detoxine has been used with some success in chronic rheumatism.

On the preceding pages three types of anti-histaminic substances have been described, namely (1) histaminase, destroying histamine by enzymic action; (2) certain amines of phenol ethers acting antagonistically to histamine in a way inexplicable so far; (3) ascorbic acid and similar reducing cell substances, preventing if abundantly present the liberation of histamine in the intracellular antigen-antibody reaction. It has to be borne in mind, however, that histamine action is only one component of the anaphylactic mechanism. Its elimination can only mitigate, not completely abolish the specific shock effect.

That, indeed, histamine reactions are distinguishable from specific anaphylactic reactions, even if they imitate the clinical picture of the latter in the closest manner, was impressively shown by Kallós and Pagel (1937) in their experimental investigations of bronchial asthma, undoubtedly an anaphylactic disease. By means of a spray apparatus producing a particularly fine mist, a condition clinically, pathologically and immunologically identical with human asthma could be produced in guinea-pigs sensitised actively or passively against an antigen, if exposed to the inhalation of the same antigen (egg albumin or horse

serum). The same type of asthma attack is reproduced in normal guinea-pigs by the inhalation of histamine or acetylcholine solutions in the form of an equally fine mist. The histological analysis, however, revealed certain characteristic differences between the two types of shock, especially the enormous eosinophil reaction in the group of the anaphylactic animals, occurring in the wall of the intermediate bronchi and leading to other severe lesions in these tissues. The authors conclude that no more than a secondary rôle can be attributed to histamine-like substances in the pathogenesis of asthma. "For the causation of the asthma complex in its totality the specific antigen-antibody reaction in the bronchus remains the indispensable condition."

Anti-rheumatic Effect of Salicylates, Bilirubin and Mineral Waters.—So far measures against the histamine part of the anaphylactic complex have been reviewed. What are the corresponding possibilities against the tissue damage caused by the total anaphylactic attack? Very little is known of means to take the sting out of the intracellular antigen-antibody reaction. It must be clearly understood that the question here is not concerned with the prevention of the reaction itself, obviously the most desirable form of anti-anaphylactic treatment. That will be discussed in Part II of this article. Here are meant the histological sequelæ of the reaction, the acute or chronic tissue effect which represents the respective anaphylactic disease. It is well known that the acute anaphylactic reaction, characterised by spastic shocks (*e.g.* fatal anaphylactic shock in experimental animals, asthma in human patients), can be alleviated or even suppressed by certain drugs. This effect, however, is merely symptomatic. The contraction of smooth muscles is prevented or paralysed as, for example, by anæsthesia, atropine, adrenaline, ephedrine, probably certain calcium salts which, moreover, inhibit exudation and secretion. No therapeutic effect can be expected from such measures in rheumatism which does not involve the acute irritation of smooth muscles.

Three groups of pharmaceutic or chemical substances, however, which possess an anti-rheumatic effect have to be considered, some of old-established reputation, one of more recent experience, but all, so far, with their action unexplained. Precedence is due to salicylates in acute rheumatic fever. Weintraud in his pioneer article of 1913 suggested an explanation in assuming a kind of narcotic action of salicylate on the specifically irritated tissue cells, similar to the effect of anæsthesia in acute anaphylactic shock. A very different interpretation was attempted and experimentally tackled by Coburn and Kapp (1943). These American investigators cite the observation by Marrack and Smith (1931) that diphtheria toxin-antitoxin floccules are dispersed by salicylate. They attach great significance to two results obtained by Derick, Hitchcock and Swift (1928) with aspirin in serum sickness: (1) the arthritis of serum sickness was prevented by aspirin which, however, had no effect on the other signs of the disease; (2) the serum of patients prophylactically treated with this

drug failed to precipitate horse serum. The conclusion that antibodies are kept on a low level by the anti-rheumatic drug is shared by Coburn and Kapp on the ground of their experiments in which they studied *in vitro* the effect of salicylates on specific precipitations. The stimulating, but not wholly convincing argument attributes the salicylate effect to an inactivation of antibody.

Bilirubin.—Another anti-rheumatic phenomenon, no less obscure, points to bilirubin. Patients with severe chronic rheumatism (rheumatoid arthritis, fibrositis) sometimes derive dramatic benefit from an attack of jaundice if the bilirubinæmia reaches a high level (Hench, 1938). I have tried to throw some light on the connection between bilirubinæmia and rheumatism by studying the effect of bile and bilirubin on antigen-antibody reactions *in vitro* and *in vivo*. The experiments were carried out in 1939 and 1940 at the Royal National Hospital for Rheumatic Diseases in Bath, but remained incomplete and unpublished. The addition of bile or bilirubin to rabbit sera with high anti-streptococcal titres (agglutinin and precipitin) did not alter the specific reactions significantly. Equally insignificant was the effect on the agglutinin and precipitin titres if the bilirubin was intravenously injected in the immunised rabbit. This was hardly surprising in view of the known fact that bilirubin injections produce only a very transient and low-grade bilirubinæmia. I therefore attempted to produce a lasting and intensive bilirubinæmia in such animals by ligation of the common bile duct. Such obstructive jaundice is tolerated by the rabbits for several weeks, even with considerable Van den Bergh values in the serum (5 to 18 mg. per cent. bilirubin). The blood samples taken at intervals after operation showed no appreciable decrease of the agglutinin, but a perhaps significant observation was made with the precipitation test, the streptococcal carbohydrate fraction being used as antigen. The tests were kept for 24 hours in the incubator and for a further 24 hours at room temperature. Before operation the reactions were mostly complete when read after the first 24 hours at 37°, and equal or only slightly stronger after the second day at room temperature. This end result, the 48 hours' reading, remained essentially unimpaired in the operated animals for 2, 3 or even 6 weeks, but the 24 hours' reaction was completely or almost completely abolished, either from the first post-operation day, when a severe jaundice occurred at once, or after 4 to 9 days according to the Van den Bergh values.

In a very few tests on rabbits subcutaneously injected with horse serum the precipitin reactions remained unchanged under moderate bilirubinæmia produced by ligation of the common bile duct, even when slightly raised by additional bilirubin injections. These last experiments, however, were not so much planned with a view to the investigation of the precipitin reaction *in vitro*, but to the observation of the local anaphylactic reaction after intradermal injection of the antigen, the Arthus phenomenon, under the influence of the biliru-

binæmia. At this stage the research was interrupted; no definite conclusion can be drawn from the two suggestive experiments which would seem to encourage further investigations on such lines. These two experiments gave the following results :—

In one rabbit the ligation led to a moderate bilirubinæmia which fluctuated during the first 17 days after operation between 0·5 and 2 mg. per cent., reached 4 mg. per cent. on the twentieth day, and then continued for the following 11 days at a level of 3 to 4 mg. per cent. Three intradermal tests carried out during these four weeks showed not the slightest difference of the Arthus phenomenon which progressed within 2 to 4 days to the typical skin necrosis. An attempt was then made to increase the jaundice by daily intravenous injections of 10 mg. bilirubin. Twenty minutes after the eighth injection the Van den Bergh gave 7 mg. per cent., falling the next day to 5 mg. per cent. The intradermal test done shortly before this eighth bilirubin injection showed a marked delay in the development of the Arthus reaction with skin necrosis not before the seventh day.

Much more striking was the result in another rabbit. This animal had served 13 months before as a test for the technique of the operation. The ligation of the bile duct had produced a prompt bilirubinæmia, rising from 3·5 mg. per cent. on the first day to 8·5 on the fourth day, then falling off (6 mg. per cent. on the sixth day, 2·25 on the eighth day, 0·5 on the eleventh and fourteenth days) to zero never to rise again. A control laparotomy one month after operation showed an extended gall bladder and bile duct. The animal survived in perfect health and free from bilirubinæmia. More than a year later it was sensitised with horse serum (7 subcutaneous injections of 3 c.c. each at intervals of about five days) until a firm skin hypersensitiveness was established to 0·1 c.c. of horse serum intradermically. Twelve almost daily injections of 10 mg. bilirubin only produced serum levels of 1·5-2 mg. per cent., if tested half an hour after injection.

The skin reaction carried out two hours before the last bilirubin injection remained negative. A slight erythema 24 hours after the intradermal injection was the sole response, and no necrosis developed. After a complete rest of 12 days and several times afterwards in intervals of 8 to 14 days the skin tests were again fully positive, with necrosis on the third or fourth day.

These observations, scanty as they are, appear to warrant a resumption of a research on anaphylactic reactions in experimentally jaundiced animals with a view to elucidating the effect of bilirubinæmia on chronic rheumatism. The deliberate production of jaundice by suitable drugs in patients with severe rheumatoid arthritis has been contemplated and discussed, but criticised and condemned in view of the obvious dangers. I am not aware of clinical trials on a scale large enough to permit conclusions.

Mineral Waters.—The last chemical representatives of anti-anaphylactic activity and anti-rheumatic reputation, though in both respects of rather doubtful character, are the group of certain natural mineral waters or springs. A strange observation was made by Billard in 1910 and followed up by many tests and experiments, mostly in France, with a few articles from Spain and Portugal (for literature,

see Mougeot, 1923, and collection of articles, 1938). I know of no similar publication from other countries. Billard and his followers advanced the claim that certain springs possess a strong anti-anaphylactic effect on sensitised guinea-pigs if injected either for several days or once shortly before the shock-releasing antigen dose is given. While the controls perish in three minutes, the prophylactically treated animals survive with an attentuated shock or no reaction at all. In several spas (*e.g.* Royat, Vichy) one or more springs possess a pronounced anti-anaphylactic power, others in close proximity have none. The effective waters from different spas have different chemical composition. It could be assumed that the effect is entirely symptomatic and comparable with the anti-spastic action of certain calcium compounds. An article by Loeper and Mougeot (1931), however, contains the statement that the mineral water prevents the phenomenon of Richet (the spastic anaphylactic shock) as well as the skin phenomenon of Arthus. I have tested the mineral water of Bath. No effect at all was observed after the guinea-pigs were injected daily or only twice during the 21 days' period between sensitisation and shock-releasing dose of horse serum. Like the controls, they all died within two to four minutes with typical dyspnœa and convulsions, and post-mortem showed the characteristic feature of lung dilatation. The experiment was carried out with the spring tapped in the National Hospital for Rheumatic Diseases.

Detoxication or Prevention of the Anaphylactic Reaction.—So far, then, no definite and reliable procedure has been established to render anaphylactic reactions harmless in their effect on the hypersensitive tissue cells. Much more apparent success has attended the various efforts to prevent the anaphylactic reaction itself. It may be asked, why has there been, and is, so much labour spent in attempts to take the sting out of the anaphylactic attack if apparently so much more can be achieved in tackling directly the root of the evil, the basic anaphylactic condition itself? The answer is this: Dramatic and lasting successes can be obtained in the latter field, but, as will be seen, they remain confined to favourable individual cases. Moreover, often enough they are of the nature of a compromise. So far the anaphylactic disposition in general and the rheumatic "diathesis" in particular can be treated with some success, but not cured. On the other hand, the alleviation of the anaphylactic reaction, though less fundamental a procedure, would constitute a universal method applicable to all anaphylactic reactions and independent of the individual patient. Such a "detoxication" would not touch the anaphylactic basis, but would cure the anaphylactic disease. Therefore the effort in this direction, though not yet crowned with any conspicuous reward, remains a sound proposition.

II. The Prevention of the Anaphylactic Reaction

A restatement of the essentials in the rheumatic condition will help to grasp the three possible avenues of a therapeutic approach. First there is somewhere in the body (or much more rarely outside the body as in gout) the source of the antigen. At the other end of the system are the sensitised cells carrying the corresponding antibody. Between these two poles there lie the stretches of the circulation insufficiently equipped with antibody to bar the way of the antigen to the tissues.

Thus it is obvious that we have three targets of therapeutic attack: (1) the removal of the antigen or the prevention of its renewed access to the patient would eliminate the " trigger " of the rheumatic reaction; (2) the removal of the antibody from the cells of the reticulo-endothelial tissue would abolish the state of hypersensitiveness; (3) increase of humoral antibodies would erect a protective barrier between the antigen and the tissue antibody.

(1) *Measures against the Antigen.*—In the comparatively simple case of an extraneous antigen, as in classical gout, a prevention of the attacks can be achieved if the antigen concerned is known and avoidable. Unfortunately these two conditions are much more difficult to fulfil than in the corresponding situation of hay fever. Many patients in the heyday of gout knew well enough the inevitable consequence of convivial excesses; but it is quite certain that neither port nor burgundy were the real antigen. It is probable that their notorious effect was only ancillary; the alcohol increased and accelerated the intestinal resorption of the particular, mostly unrecognised part of the diet to which the body was sensitised.

In the great majority of rheumatic patients the antigen is of bacterial origin, and is present at the site of focal or otherwise chronic infection. What are the chances of a complete removal or at least substantial reduction of such a source of antigen? The complete removal is more often than not a pious proposition, but hardly ever necessary. The quantitative factor has always to be borne in mind. A certain quantity of neutralising antibody is mostly available in the circulation once the primary attack has subsided, and sufficient to cope with a limited amount of antigen. A flare-up of the persisting infection or a fresh invasion, however, overwhelms the mediocre barrier, and a new rheumatic attack or an exacerbation of chronic rheumatism follows the renewed contact of the antigen with the intracellular antibody.

Two main means are at the clinician's disposal to deal with the infective antigen: the operative elimination of grossly infected sites such as tonsils, teeth, gall bladder, appendix, and the anti-bacterial effect of chemotherapy or chemoprophylaxis. There is no doubt whatever that countless patients after their first attack of rheumatic

fever have been saved by timely tonsillectomy, that chronic rheumatic patients have been improved by a gall-bladder operation, extraction of teeth, appendectomy. The very great number of failures, on the other hand, are due to the inevitable co-infection of lymph nodes and mucous cavities inaccessible to the surgeon's knife. Great hope has been attached to the discovery of effective chemotherapeutic agents, *e.g.* the anti-streptococcal sulphonamides. Unfortunately these new drugs, including penicillin, are not yet effective enough against the microbes in their chronic varieties. One day, no doubt, improved remedies will possess a wider range of efficacy embracing the more resistant forms of the infective agents and penetrating more deeply into the walled-off sites of chronic infection. Even now, however, much can be achieved in certain groups of rheumatic disease by the chemotherapeutic prevention of recurring acute infection. After a primary attack of rheumatic fever following a streptococcal sore throat the average patient recovers so far as to regain a *modus vivendi* in a sort of precarious equilibrium with the chronic residues of the initial acute infection, but at any moment a fresh invasion might sweep him off this slippery foothold. If such a recurring infection with its sudden increase of antigenic influx could be prevented by means of a permanent chemoprophylactic medication, the ever-threatening peril of a relapse would be minimised or eliminated. That, indeed, has been accomplished in America with a most gratifying degree of success, especially after the original three-months' break of the sulphanilamide administration late in summer had been abandoned and 1·3 gm. of the drug was given in two equal doses day by day without interruption (Thomas, France, and Reichsman, 1941, and C. B. Thomas, 1942. See also the leading articles, *Brit. Med. Journ.*, 1941 and 1942). This great success concerns acute juvenile rheumatism and is strictly confined to prophylaxis in the dormant interval between the attacks. Therefore, no similar results can be expected in chronic rheumatism which corresponds with the attack stage of rheumatic fever, equally refractory to the anti-streptococcal drugs.

(2) *Measures against the Cell-fixed Antibody.*—In the years after 1920 remarkable results were obtained in the State Serum Institute in Copenhagen with metal salts during immunisation, summarised in several publications by Madsen (1923, 1924). Walbum and Mörch (1923) had found that the amount of antibodies appearing during vaccination in the serum of experimental animals was enormously and rapidly increased after the injection of certain metal salts, especially manganous chloride ($MnCl_2 . 4H_2O$) and beryllium chloride ($BeCl_2$). This sudden increase of the antibody level in the blood was also observed when the metal salt was injected long after the last vaccination dose at a time when no antigen could possibly have been left in the organism. The Danish research workers encountered the phenomenon in all types of immunisations tested; considerable antibody titres were obtained in horses, rabbits, goats, *e.g.* antitoxins (diphtheria and

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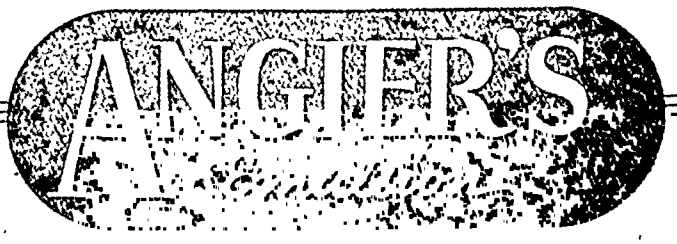

tetanus), agglutinins (coli), amboceptors (sheep blood hæmolysin), bacteriotropins (meningococcal). Occasionally one or the other animal did not respond to the metal treatment which is given intravenously, administration *per os* being without effect. The increase of the serum antibody follows the metal injection within a few hours, rising in a steep curve to a maximum, while the metal salt disappears with corresponding rapidity from the blood. Of paramount importance is the optimal dose of the drug as exemplified with $BeCl_2$ in rabbits previously injected with sheep erythrocytes after the hæmolysin titre had settled :

0·0002 molar	—No effect
0·0003 ,,	—Distinct increase
0·001 ,,	—Optimal increase
0·01 ,,	—Less optimal increase
0·1 and 1·0 molar	—Decrease and later death of animal.

Neufeld and Meyer (1924) confirmed the Danish results by a single but most impressive experiment on mice immunised with pneumococci ; the serum of the animals, bled 6 or 9 hours after the last of four daily injections of $MnCl_2$, possessed a very high titre of protective antibody, never obtainable even in hyperimmunised mice without the metal salt.

These observations taken all together suggest that the action of the metal salt concerns not so much, if at all, the formation of antibody, but its shedding from the cellular stores into the circulation. It would, therefore, seem that the method opens an ideal way to tackle the rheumatic trouble and other anaphylactic conditions at the very root, the faulty distribution of antibody. It would remove the bulk of the antibody from the tissue cells and increase the antibody barrier in the circulation. Almost overnight the critical state of imperfect immunisation or hypersensitiveness would be transformed into a state of perfect immunity.

The first experiment on anaphylaxis was reported by Pico (1924), who, however, was considerably less successful in his studies on the metal effect on immunisation ; with the exception of diphtheria antitoxin, where Pico obtained a moderate increase in some horses, he failed to produce any effect in all his other tests. His anaphylaxis experiment was performed on 35 guinea-pigs sensitised against horse serum ; they received the injection of $MnCl_2$ 1 to 4 min. before the shock-provoking dose of the antigen : 12 animals survived with no or a very light shock, while 23 died with typical symptoms. More successful was Klopstock (1925) in two experiments on a few guinea-pigs ; he could save all the animals, when an interval of 2 to 8 hours was kept between the injection of the manganous chloride and the shock dose of the antigen, even if the fatal dose was doubled.

All these results would pave the way for an entirely new therapeutic approach to rheumatism, if it were possible to reproduce in man the striking successes in experimental animals.

However, an inexplicable development has brought this line of procedure to a sudden and complete deadlock. When I tried in 1938 to reproduce the antibody-increasing action of $MnCl_2$ and $BeCl_2$ in rabbits and failed, I was, although warned by Dr Madsen in a private letter, unaware of the dramatic turn of events described by Walbum in 1934. His admirable article gives first a condensed summary of the whole subject with all the clear-cut results obtained in Copenhagen and confirmed elsewhere, including the many chemotherapeutic experiments with metal salts in a number of infections and intoxications. It is true that single animals had sometimes failed to respond; the mainly negative results of Pico (1924) have been mentioned; in the same year McIntosh and Kingsbury reported their failure in a small series of attempts to raise the titre of sheep cell amboceptor and typhoid agglutinin in rabbits by beryllium chloride. The Danish team, on the other hand, continued to accumulate a large body of evidence in the positive sense, and in Denmark and Germany the commercial production of therapeutic sera at several places made use of the manganese treatment in diphtheria horses with apparently good results. The period of these various successes with metal salts covered the years 1920 (the first experiments were done at the end of 1919) till 1925. In 1926-27 the first irregularities and temporary setbacks were encountered, simultaneous with the complete breakdown of the sanocrysin effect on tuberculosis in rabbits, so promising in the preceding year. Some improvement in the results could still be achieved in 1927-29, but from 1930 onwards and all through the following four years every single experiment failed, and not one of the former positive results could be reproduced in large-scale investigations with the same species of animals used before. Moreover, at the same time the well-known effect of other non-specific substances such as Witte peptone, casein and gelatin on immunisation was retested and found to be completely lacking. All attempts to elucidate this total change, with special attention to nutritional factors, have so far failed. We are faced "with the strange phenomenon that the mammalian organism is no longer able to increase by non-specific means its defence against bacterial infections and bacterial toxins."

From this dramatic episode of modern research work by eminent investigators over a period of 15 years, with far-reaching hopes dashed to ruins, we turn to the classical method of abolishing or mitigating the dangerous state of specific hypersensitiveness by desensitisation. The notion of "desensitisation" has been derived from often-confirmed experiments on sensitised guinea-pigs. If subjected to the anaphylactic shock by re-injection of the antigen in so small an amount that they develop only a mild shock and recover, the animals are subsequently found to be no longer hypersensitive even to large doses of the antigen. This state of "anti-anaphylaxis" may last for weeks, to be followed by a new stage of anaphylactic hypersensitiveness responding to intravenous reinjection with severe shock, or may

remain permanent so that even a fresh subcutaneous injection of the antigen with the purpose of re-sensitising fails to recreate the anaphylactic state. The original explanation of the phenomenon visualised only one of two quite different mechanisms: it was assumed that the first, tolerated, shock used up the whole amount of cell-fixed antibody and thus left the surviving animal free of hypersensitiveness. However, this temporary removal of the cell-fixed antibody by neutralisation, this short-lived "negative phase," could not possibly account for the long duration of the anti-anaphylactic phase. Obviously, still another and more permanent mechanism is called forth; the repetition of the antigen injection acts as a strong stimulus to antibody formation, this time intensive enough to lead to a surplus production nearer to perfect immunisation with substantial amounts of circulating antibody. It is this completed immunisation that accounts for the duration of the anti-anaphylaxis; the latter becomes permanent when the slow excretion of the antibody from the circulation in the resting animal proceeds apace with its shedding from the tissue cells, or it persists at least for a considerable time, until the blood antibody has been lost again, but still sufficient cell antibody remains to re-establish the condition of hypersensitiveness. Urbach (1935) has lucidly distinguished the two mechanisms, frequently confused. He calls the first and immediate effect, the neutralisation of the cell-fixed antibody, "deallergisation," and reserves the term "desensitisation" for the second, more slowly developing, but lasting, effect, the increase of the free circulating antibody. This second effect in the direction of perfect immunity will be considered in the last heading. Here, where the problem of antibody removal from the tissue cells of a rheumatic patient is under review, only the mechanism of deallergisation has its proper place. No doubt, such an immediate, but transient neutralisation of cell antibody is practicable. For example, it plays its legitimate and important rôle in serotherapy when good reasons make it probable or tests have proved that the patient to be treated with therapeutic serum is anaphylactic as a result of previous treatment with the same species-specific serum (horse). The direct injection of the full serum dose, even subcutaneous only, could lead, and if given intramuscularly or intravenously, would lead to a prompt anaphylactic collapse. If, however, the serum is first given intradermically in smallest amounts and repeatedly at short intervals until no local reaction appears, then in several small subcutaneous injections, deallergisation is soon accomplished and the patient is ready for the full therapeutic dose, to be safely administered by any route. This well-established practice has certainly prevented many serious accidents and has saved life. In anaphylactic disease a corresponding procedure has but a very limited chance. In hay fever, where the patient is subjected to a sudden and predictable exposure to the antigen (air-borne pollen) comparable to a serum injection, a treatment with pollen extract by small and frequent intradermal injections, closely preceding the pollen season, could

deallergise the tissues for a short period. What, however, could be expected in rheumatism with its permanent exposure to the endogenous antigen? Is the continuous injection of antigen (*e.g.* in the form of a specific vaccine in subreactive amounts), literally continuous, day and night, a sensible and practicable proposition? Definitely No! The impracticability is obvious. A simple argument, moreover, shows that the idea is even not sensible. The rheumatic patient is not threatened by a massive antigen influx against which he has to be protected, but he suffers continual micro-shocks in his sensitised tissues produced by minimal amounts of antigen. That is his disease, and exactly such cellular micro-shocks would be produced by the deliberate administration of the antigen. A "therapy" of this kind is bound to elicit an exacerbation of the condition. A further and still more serious consequence of a "successful" deallergisation in rheumatism must be borne in mind. In sensitisation to a therapeutic serum or grass pollen (hay fever) or cat's hair, house dust, moulds (asthma) the antibody has no useful part to play; its removal from the tissue cells involves no risk whatever. The rheumatic patient, however, benefits from these cellular antibodies in so far as they equip him with that degree of anti-infective or antitoxic tissue immunity which prevents the unchecked spread and generalisation of the persisting focal infection. To these antibodies he owes the chronic or dormant character of his infection. Their removal would deprive him of the last shred of hard-gained semi-immunity and deliver him defenceless to the assault of the unleashed micro-organism. Cured of his rheumatism he would succumb to generalised infection and sepsis.

Deallergisation has no place in anti-rheumatic therapy.

(3) *Measures for an Increase of the Humoral Antibody.*—There remains one last approach to a cure of rheumatic disease: the attempt to break the state of hypersensitiveness by an increase of humoral antibody, by desensitisation in the correct meaning of the word, leading away from the precarious state of semi-immunity and sensitisation nearer to the haven of perfect immunisation. The crux lies in the very cause of rheumatic disease, the basic debility of the reticulo-endothelial system in its response to antigenic stimuli. However, the extent of this reticulo-endothelial dysfunction differs from patient to patient and periodically in one and the same patient under the changing conditions of his general health. In one patient the damaged or constitutionally inferior system may be below any hope of repair, whereas his fellow-sufferer might be much nearer the threshold of normal reactivity. In the first patient any therapeutic endeavour would be doomed to failure, in the second one a single effort might tip the scales. This variety of rheumatic reactivity is reflected in the wide range of medical experience from triumph to heart-rending disappointment. That is the fascination and exasperation in the profession of the rheumatism specialist.

The ideal cure of rheumatic disease, the sole truly ætiological

therapy, would be the full restoration of the antibody-producing organ. In all diseases the damaged part of the body is only one district in a complex system, interacting with every other province and dependent on the condition of the whole. Harmful factors of any kind, particular and general, have their effect on the remotest spheres. Malnutrition, physical strain, endocrine disturbances are soon reflected in many indirect incapacitations, including the deterioration of the response to immunising agents. Spiritual suffering, emotional tension, the slings and arrows of outrageous fortune, the heartache and the thousand natural shocks that flesh is heir to—these translate themselves into disturbances of many, if not all, physiological functions. I hear that a fractured bone can be well cured without much regard for the patient's matrimonial worries. In the rheumatic patient the entire standard of life, physical and spiritual, is of paramount importance. I wonder how many spa courses derive their beneficial results more from such general factors as removal from the humdrum of daily life, fresh revitalising experiences, the change of the mental climate in hotel or hospital, and the suggestive power of a clever spa doctor, than from the magic effect of the springs.

There are, of course, quite a number of more direct means for the activation of the reticulo-endothelial function. Two main groups can be distinguished, although it is possible that their mechanisms are not as different as they would seem at first sight: the general stimulation by a physico-chemical goad, and the particular impact of an antigenic agent.

Physico-chemical Stimulation.—The now classical instrument of physico-chemical stimulation is gold. The precise mechanism of gold salt therapy is unknown. The statement that it " arrests and lessens inflammation " is pretty meaningless. Gold salts have no microbicidal effect, and their efficacy in chemotherapeutic experiment is interpreted as due to the stimulating action on the reticulo-endothelial system and the accelerated mobilisation of the natural defence forces. Careful studies in America (Freyberg, 1942) have furnished many important data. The three best gold compounds, all with a gold content of 50 per cent., are auro-sodium-thiomalate (myocrisin), auro-calcium-thiomalate, and auro-thioglucose (solganal B). Their retention in the body is of long duration, lasting from one to ten months according to the dose injected. The trouble in gold therapy is the considerable toxicity of all the therapeutic preparations with their well-known skin, blood and kidney reactions. These reactions can be much diminished and mitigated by a decrease of the dose. Freyberg rejects the dose of 0·1 gm. containing 50 mg. of gold as too toxic and recommends 0·05 gm., equal to 25 mg. of gold, as the dose of choice. Reactions after this optimal medication still occur in 17 per cent. of the cases, but are not severe.

A similar chemical stimulation can be induced by means of sulphur.

Experienced specialists have seen their best results with a combination of gold and sulphur, popular in France, if I remember correctly.

The beneficial effect of these chemical stimulants in many cases of chronic rheumatism is a universally accepted fact. Their failure in other cases will astonish nobody who correlates the chance of these drugs with the degree of reactivity in the individual patient. Moreover, this type of stimulation consists in irritation, and the borderline between mild and severe, between beneficial and harmful, is indistinct.

Somewhat allied to the mechanism of gold and sulphur action is the method of protein shock. Here the stimulation is produced by *intravenous* injection of protein (casein, vaccines), and releases a heavy general reaction with fever and intense malaise. The widespread reluctance to employ the dangerous procedure, too close to harmful irritation, can be well understood.

Antigenic Stimulation.—The most natural and direct approach to reticulo-endothelial activation would appear to be the antigenic stimulation. Antigens are all substances that provoke the formation of antibody. Their inoculation, covered by the term immunisation in the wider sense of the word, is carried out in a way which avoids any strong reaction, local or general, and is frequently repeated at suitable intervals with the definite purpose to act as the appropriate stimulus on the organ whose special function is the formation of antibody.

In rheumatism the formation of antibody as such fulfils no useful purpose. The essential goal is the increase of the ætiologically specific antibody, anti-streptococcal in the large majority of cases. What, therefore, would seem more rational and inviting than the plan to increase this antibody and to transform the anti-streptococcal hypersensitiveness into perfect immunity by means of a specific vaccine, made from hæmolytic streptococci, preferably the autogenous strain. A little reflection, however, should show the futility and dangerousness of specific vaccination. The rheumatic attacks are due to the antigen which enters the system from the site of chronic infection. The patient has demonstrated by his illness his inability to give to this antigenic stimulus the adequate antibody response. On the contrary, the antigen acts as permanent fuel to his anaphylaxis. Increasing this fuel by an additional dose of the same antigen in the form of the corresponding vaccine is bound to rekindle the smouldering flame. That is the danger of *specific* vaccination in rheumatism. The futility of the scheme is equally obvious to the thoughtful therapist. No artificial method of inoculation could surpass the natural vaccination in small and continuous dosage from the antigen depôt carried by the patient. Where this ideal vaccination has not succeeded in achieving the desired effect, what could be expected from the doctor's syringe? Curious efforts are sometimes witnessed by a bacteriological laboratory. Time and again the bacteriologist receives tonsils just removed from a rheumatic patient with the request for an autogenous vaccine. I

should like to understand the reasoning which underlies such a request. Obviously, perhaps rightly, the doctor has regarded the bacterial flora in these septic tonsils dangerous enough to justify the removal from the patient's body by a serious operation. This done, he proposes to return to the patient, hardly delivered from the evil, the dreaded poison. Though this be method, yet there is madness in it.

In fact, these reflections are amply borne out by experience All too many patients have had to pay for a wrong treatment with serious exacerbations. Lucky those whose instinct revolted after the first few injections before irreparable damage had been done. I wish to maintain with the greatest possible emphasis that streptococcal or other *specific* vaccines are strictly contraindicated in rheumatism.

Yet I am convinced that vaccination has a wide field in rheumatic disease, especially in all forms of chronic rheumatism. There is plenty of experimental evidence that the inoculation of combined vaccines favourably influences the response to the different components. The combination treatment, for example T.A.B. combined with tetanus toxoid, or a whooping-cough vaccine combined with diphtheria toxoid, has in experiment and practice proved its value, even in the case of the poor responder. The rheumatic patient already receives one kind of vaccine, the specific antigen, from his own focus. To combine this immunising agent with another *non-specific* antigen, given by injection, is a rational proposition, borne out by striking results in many cases.

Indeed, one of the oldest observations of this kind has been derived from experience. Bee-keepers are credited with immunity against rheumatism. The accidental exposure to bee-stings has been claimed to improve rheumatic disease. The therapeutic injection of bee venom enjoys the reputation of an excellent anti-rheumatic measure. More recently the use of snake venom has been added to the armamentarium. These venoms are given intradermically in small amounts, sometimes simultaneously at several places, and frequently repeated. The inconvenience, the local irritation and painfulness hamper a large-scale adoption of the method.

Much easier for patient and doctor, free from any risk, with promising and sometimes remarkable results, is the administration of non-specific vaccines on the established lines of optimal technique. Certain commercial preparations have been issued for the purpose, omnadin being the best known amongst them, but not available at present. The use of the ever-ready T.A.B. vaccine has been recommended, but is not very popular because of the frequent unpleasant reactions. I prefer a more all-round mixture of organisms, to be freshly prepared and open to adaptation for the individual patient. Organisms present in great number in the patient's throat or nasopharyngeal cavity should be omitted to safeguard the strictly non-specific character of the vaccine. The following formula, combining a gram negative bacillus, a gram positive bacillus, a gram negative coccus, a gram

positive coccus, may be recommended without the claim of particular superiority :—

Pneumobacillus Friedlaender	200 millions per c.c.
C. Hofmann	200 „ „ „
M. catarrhalis, smooth	300 „ „ „
Staph. aureus mixed (oral)	300 „ „ „

The Micrococcus catarrhalis is the very rare pathogen discovered by Pfeiffer in a case of severe bronchitis and characterised by the smoothness of the colony ; it must not be confused with the ubiquitous rough varieties. If a preliminary throat culture reveals for instance Friedlaender or Staph. aureus in abundance, they should be replaced in the vaccine by H. influenzæ 500 millions per c.c. and pneumococci (several types mixed) 200 millions per c.c. respectively. The vaccine is given subcutaneously, beginning with 0·1 c.c., at strict intervals of seven days and with increasing amounts up to the maximum of 2 c.c. in such a way that any strong reactions are carefully avoided. The warning signal of too high a dose is a local reaction stronger than a pink area with slight induration and soreness to touch, appearing 12 to 20 hours after injection and fading during the next day, and any systematic reaction such as marked malaise, rise of temperature, headache, insomnia. The treatment should be supported by the prescription of ascorbic acid tablets, 100 mg. daily and 200 mg. on the day of the vaccination. The patient has to be instructed how to take the tablets so that a substantial loss of the drug by oxidation is prevented. It is wrong to chew or to suck the tablets, they must be swallowed intact. The destructive effect of tannic acid from coffee and tea must be avoided by proper timing of the intake.

The vaccination is continued for many months, in rheumatoid arthritis not less than nine months, even when considerable improvement has occurred much earlier. Then a rest period of three months may be tried in order to enhance the patient's reactivity to a second course. Premature discontinuation on the strength of an early success may be followed by discouraging relapses. The co-operation of the patient, in most cases readily given after the pleasing and promising effect of the first weeks, should be maintained by timely warnings not to take an early improvement as the end result and by a firm and hopeful attitude. The psychological factor is a priceless tonic in rheumatic disease.

Summary and Conclusion

This review of therapeutic possibilities in rheumatism, based on the anaphylactic theory of the disease and assuming a functional debility of the reticulo-endothelial system in its response to antigens as the basic cause, is not concerned with symptomatic methods of treatment. Hydrotherapy, radiation and heat, the invaluable work of the surgeon and orthopædist, lie outside the scope of this article.

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* *Brit. Med. J.*, 1942, 1, 668.
J. Clin. Endocrin., 1942, 2, 639.

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Many lines remain open for future research. For the time being little more than two procedures seem to offer a reasonable promise of success. In rheumatic fever the chemoprophylactic prevention of recurring infection holds a high place amongst all measures of after-care. In chronic rheumatism a long-term vaccination with a strictly non-specific vaccine deserves a trial. The significance of vitamin C in sensitisation and immunisation has been discussed and the conclusion drawn for therapeutic procedure.

I have often pondered over the possibility of a new and truly ætiological approach to anaphylactic disease in general and rheumatism in particular. The speculative nature of the following reflection is not denied.

The mesodermal tissue of the body, the reticulo-endothelial system, represents the organ of antibody production. The mechanism of antibody formation and output has been brought nearer to our understanding by some investigators. I should like to draw special attention to the experiments by Florence Sabin and her most illuminating article (1939). Little, however, is known of the physiology of these cells which enables them to carry out their function. Madsen has always proffered the conception of antibody formation as a secretory process, enzymic in nature. This function could be compared with the function of endocrine glands, and it seems possible that a hormone-like factor, specific to these cells, is essential for their unimpaired activity. The functional disability of the antibody-producing cell system could be attributed to a deficiency in such a "reticulo-endothelial hormone." On the other hand, healthy and vigorous cells of this system would be distinguished by an abundance of the hormone. Certain organs, especially the spleen, are rich in reticulo-endothelial cells; their importance in immunisation has been experimentally demonstrated. Splenectomy, alone or together with the temporary paralysis of the widely scattered reticulo-endothelial cells by means of blockade, frustrates the effect of active immunisation (Neufeld and Meyer).

I wonder whether such a hormonal factor could be extracted from young and healthy spleen tissue and used in a "substitute therapy," after the model of insulin in diabetes, on patients suffering from a reticulo-endothelial dysfunction.

The realisation of such a dream would even surpass the efficacy of other substitute therapies. The diabetic patient has to be kept under insulin administration for his lifetime. The rheumatic patient would be cured not of his basic debility of the reticulo-endothelial system, but of his actual anaphylactic condition, once the balance between antigen and antibody had been established in a state of perfected immunisation.

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THE FUNCTIONS OF THE STOMACH IN RELATION TO THE TREATMENT OF PEPTIC ULCER *

By C. F. W. ILLINGWORTH

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UNTIL towards the end of last century peptic ulcer was somewhat of a rarity. Since then year by year its incidence has increased, so that it is now one of the commonest causes of prolonged disablement. But this great increase in frequency has been accompanied by no commensurate improvement in therapy. Indeed, the treatment of peptic ulcer now is not greatly different from the treatment practised fifty years ago. In an age which has seen many notable therapeutic discoveries and a vast improvement in many fields of medicine and surgery the problem of peptic ulcer remains unsolved.

It would, of course, be an exaggeration to suggest that the present-day treatment of ulcer is entirely ineffective. It is true that many ulcers heal under careful and sustained medical care; it is true that lasting cures have been achieved in selected cases by operation. But neither medical nor surgical treatment is uniformly successful; indeed, on a long-term assessment both methods fail in over 40 per cent. of cases to effect a cure.

There is thus no room for complacency, but on the other hand every reason for profound dissatisfaction. Under these circumstances it seemed to me that a review of the whole situation is called for. And since peptic ulcer is so closely related, in its origin, progress, symptomatology and treatment, to the abnormal activity of the stomach, it seemed to me that a study of the normal activity of that organ might provide the most fruitful line of approach.

Our knowledge of these functions has come from the work of many observers; from the physiologists, among whom Pavlov stands pre-eminent, and from many clinical experimentalists who have sought to solve these problems by studying them in man.

The first such study was made over a hundred years ago. It originated in two senses by accident; the unlucky accident by which Alexis St Martin, the young Canadian voyageur, sustained a musket wound of the stomach and the lucky accident which brought him to the medical care and scientific curiosity of Dr William Beaumont, who nursed him back to health, maintained and protected him for many years, and subjected him to many interesting and ingenious experiments.

* A Honyman Gillespie Lecture delivered in the Royal Infirmary on 18th January 1945.

Beaumont was concerned mainly with the process by which food reaching the stomach is converted into chyme. Since then this digestive process has been elucidated by biochemical researches on the enzymes and by many clinical observations on the acidity of the gastric juice. We now know that the stomach elaborates at least two enzymes—pepsin and lipase, and possibly a third, rennin—and churns them up with the food. We know that pepsin, with which we are most concerned, is activated by hydrochloric acid secreted by the parietal cells in the fundus and body of the stomach. Furthermore, we know that the secretion is stimulated by two mechanisms, the nervous mechanism which yields the appetite juice and the local mechanism, possibly hormonal, which comes into action when food enters the stomach. It is my purpose to review what is known of these functions in so far as they relate to peptic ulcer.

THE ACID SECRETION.—Peptic ulcer occurs only in those parts of the alimentary tract which are exposed to acid gastric juice. It is generally related to hyperchlorhydria and is practically unknown in achlorhydria; consequently it is not surprising that in the past the greatest attention has been paid to the secretion of hydrochloric acid.

As a result of test meal examinations, a great deal is known about the variations in gastric acidity in disease, for example the hyperchlorhydria of duodenal ulcer, the climbing curve of pyloric stenosis, the hypochlorhydria of gastritis, the achlorhydria of pernicious anæmia and gastric carcinoma. Curiously enough, however, until quite recently but little was known about the equally great variations which occur in health. Clinical workers are always more interested in disease than in health, just as physiologists are more interested in mice than in men.

Recently Vanzant and his colleagues at the Mayo Clinic have published their findings in a series of over 3000 healthy persons, and have brought to light several important facts. They show that the average level of gastric acidity varies at different ages and in the two sexes. In childhood the acidity is low, it rises rapidly in adolescence, maintains a high level till about the age of forty and then diminishes. In females throughout life the acidity is lower than in males. It is interesting to note that the incidence of peptic ulcer varies in just the same way, and one is tempted to speculate on a possible relationship as cause and effect.

Another interesting observation from these Mayo Clinic figures is that complete achlorhydria is quite common in perfectly healthy persons. Its incidence also rises with increasing age. In youth, achlorhydria is rare, but by the age of sixty years it is very frequent—in 23 per cent. of men and as many as 28 per cent. of women. If we knew why this progressive reduction of acidity occurs, it would be a short step to the cure of peptic ulcer.

Most methods of treatment aim at neutralisation of the acid, and a great deal of research has been undertaken to determine the relative

advantages of different drugs and diets from this point of view. It is well known that of the alkalies in common use sodium bicarbonate and magnesium oxide are quite the most effective as neutralising agents, but unfortunately their effect is short lived, and moreover they rapidly stimulate a fresh flow of acid juice. Moreover, sodium bicarbonate, which enjoys wide popularity owing to the rapidity with which it relieves pain, has the further disadvantage of leading to the production of gas, which causes distension discomfort and is very apt to encourage the objectionable habit of aërophagy. The heavy carbonates are somewhat more prolonged in action, as are aluminium hydroxide and the trisilicates, but any of these substances to be completely effective must be administered continuously by night as well as by day, and this is only practicable in hospital in-patients. Indeed, the only effective method of bringing about a complete and permanent reduction of acidity is by the operation of subtotal gastrectomy, and this method too is not universally practicable.

We must not assume, however, that the acid is the only factor concerned in peptic ulcer or that neutralisation of the acid is the essential part of treatment. There is a risk that the ease of estimation of acidity may focus too much attention on this factor to the neglect of others equally or even more important. There is indeed strong evidence that hyperchlorhydria is not so all-important as has been supposed. It is true that hyperchlorhydria is the rule in duodenal ulcer, but in gastric ulcer the acidity may be normal or even low. The usual explanation, that in gastric ulcer hyperchlorhydria is masked by the presence of mucus, is far from convincing. It should be remembered also that increased acidity does not necessarily bring increased digestive activity, for pepsin has an optimum level of hydrogen-ion concentration, and an increase above this point does not enhance its action. Lastly, the rapidity with which surgical wounds of the stomach unite indicates that even a high degree of acidity does not necessarily delay healing.

GASTRIC MOTILITY.—A peptic ulcer may quite properly be regarded as one type of wound of the stomach, and in our treatment we should bear in mind the cardinal principles which govern the healing of wounds. One of these fundamental principles is to put the part at rest. It is therefore important that we should study the movements of the stomach and the methods by which they may be controlled.

The gastric motility can be studied best by means of a balloon introduced at the end of a stomach tube and connected with a tambour recording on a moving drum. Records obtained in this way * show that the stomach is normally in a state of tone, and that small variations in the degree of tone are occurring constantly. Moreover, every two or three minutes the stomach undergoes contractions which show

* These records and all the observations on gastric motility to which I shall refer are the work of my colleague, Mr A. W. Kay, to whom I am indebted for permission to quote them.

themselves as rhythmic waves lasting for perhaps 20-30 secs., with intervening periods of quiescence. These movements are quite distinct from the so-called hunger contractions which occur in groups at long intervals and only when the stomach has been empty for a long time.

Thus the normal stomach is never completely at rest. Still less is the stomach of a patient with an active ulcer. Here the tonus variations are more marked and there is a striking increase in the frequency, amplitude and duration of the rhythmic contractions, which may even assume a tetanic character. When we picture this powerful viscus in continuous writhing activity, day and night, the surprising thing is not that ulcers resist treatment but that any ulcer ever contrives to heal in the face of such persistent irritation and trauma.

VASCULARITY OF STOMACH.—Some recent observations by two New York workers, Wolf and Wolff, have thrown a flood of light on the normal mechanism of the gastric functions. These workers like William Beaumont made their observations on a patient with a gastric fistula. The part of their work which has attracted the greatest notice related to the effect of emotional stresses on the stomach, and I shall refer to this shortly; but in addition they made many other observations on the behaviour of the stomach under normal conditions and in response to various stimuli. In their patient the gastrostomy wound was large and lax, and a ring of mucous membrane protruded through it, so they were able to view the mucosa directly as well as to test its motility and secretion. They observed that under various conditions the vascularity of the stomach varies enormously. Normally it is pale yellowish red, but it may become congested to a brilliant scarlet. Moreover, there is a certain correlation between the vascularity of the stomach, its acid secretion and its movements; the more blood coursing through it, the higher the acid and, in general, the greater the motility. This doubtless explains why mustard, highly spiced articles and the fatty acids of fried foods, which produce an intense hyperæmia, are so harmful to the healing of an ulcer and so apt to aggravate the pain.

THE NERVOUS CONTROL OF GASTRIC FUNCTION.—It has long been known that both the secretion and the motility of the stomach are subject to the influence of stimuli from the central nervous system. These stimuli are transmitted mainly by the vagus nerves and they are now known to emanate from the parasympathetic centre, which has been shown (Beattie, Sheehan and Kerr; Heslop) to be located in the anterior part of the hypothalamaus in the floor of the 3rd ventricle. That these nervous connections have an importance in relation to peptic ulcer is shown by the observation, first made by Cushing and confirmed by other neurologists (Dott; Ask-Upmark) that an acute bleeding or perforating ulcer may develop rapidly after operations in the hypothalamic regions.

Even more important in relation to the generality of peptic ulcers is the influence of nervous stimuli from the higher centres of the

cortex. It has been recognised for some years that peptic ulcer occurs commonly in a particular type of patient, the over-conscientious, active, energetic patient whom the psychologists label as " obsessional." The explanation of this incidence is supplied by the work of Wolf and Wolff, to which I have already referred. They found that in their patient the vascularity of the gastric mucous membrane, its acid secretion and its motility all varied according to his emotional state and were particularly great in those conditions of suppressed annoyance and worry to which our ulcer patients are particularly subject. It seems clear that in such circumstances there is a continuous discharge of nervous impulses from the higher centres to the hypothalamus and thus to the vagus and stomach, which lead to hyperchlorhydria and spasm and thus prevent the healing of the ulcer.

DENERVATION OF THE STOMACH.—In view of this evidence it would seem reasonable to explore the possibility of influencing the gastric secretion and motility by cutting off these nervous impulses. This has indeed already been done, but only to a very limited extent. The literature was reviewed by McCrea in 1925, later by Edwards, and more recently by Weinstein. It will be sufficient to say that while the method has been used in a considerable number of cases in the treatment of various functional disorders, there have been few observations on its use for peptic ulcer, and those few observations have been invalidated by the fact that in every case the nerve section has been combined with gastro-enterostomy or a similar procedure.

The nerve supply to the stomach has been described in detail by McCrea. Briefly, the parasympathetic fibres reach the stomach in the two vagus trunks, which lie respectively in front of and behind the lowest part of the œsophagus. At the cardia they incline towards the lesser curvature, pass down in the lesser omentum and give off branches which go to supply the stomach as far down as the pyloric antrum. The pylorus is supplied by a separate branch of the left vagus which leaves the main trunk close under the diaphragm and proceeds high in the lesser omentum towards the *porta hepatis*.

Technically it is feasible to divide the vagus trunks as they lie on the lowest part of the œsophagus, but the posterior trunk is somewhat difficult of access and there is a certain danger of puncturing the thin-walled œsophagus. It has been shown, moreover, that some parasympathetic fibres approach the stomach via the sympathetic plexuses which accompany the main vessels to the stomach, so for completeness as well as for technical ease it is preferable to perform the denervation at a lower point and to include both sympathetic and parasympathetic fibres. This is achieved by the operation of Latarjet. At the cardia, the fibres accompanying the coronary artery are cut across, and the division is carried down to the mucosa on the lesser curvature and for an inch or two over both surfaces of the stomach in order to include all vagus fibres. At the pylorus the free margin of the lesser omentum is cleared and also all nerve fibres accompanying

the right gastric and gastro-epiploic arteries. In this way an almost complete section of all the extrinsic nerves is achieved.

RESULTS OF DENERVATION OF STOMACH.—Since to interrupt the nerve supply to the stomach is a simple and safe procedure, I have felt justified in advising it, as an experiment, in selected patients as an alternative to the much more formidable operation of gastrectomy.

I have now carried out this operation in four cases, three with active duodenal ulcers, the fourth with a gastric and a duodenal ulcer. In each case a full investigation of gastric motility and secretion was made before operation and after operation.

The most striking effect has been seen in the motility of the stomach. In all four cases before operation the movements were very active, with frequent powerful rhythmic contractions and only brief intervening periods of quiescence. After operation in every case this state of unrest was replaced by almost complete immobility, with only occasional very slight alterations of tonus to disturb the calm.

In three of the cases the opportunity was taken to observe the effect of prostigmine, which is known to act by parasympathetic stimulation. Prostigmine before operation, as was to be expected, increased the gastric contractions, but after operation its effect was almost completely abolished.

An interesting observation was also made in one case on the effect of smoking. In the normal stomach, smoking has no obvious effect on the stomach movements. In the ulcer case before operation, on the other hand, it caused increased contractions accompanied by pain, and also brought about a rapid outpouring of acid juice. After operation all these results were abolished; there were no muscular contractions, the secretion was not raised and pain remained completely absent.

The effect of the operation on the acid concentration of the gastric juice at first sight appeared disappointing. While the test meal records all showed a somewhat lower acidity after operation, the reduction was not significant, and certainly quite insufficient to control the peptic activity of the juice. It is clear, as was indeed to be expected from physiological observations, that as long as the parietal cells remain active and the intrinsic nerve plexus is unimpaired the secretion of hydrochloric acid can proceed independently of external stimulation. When, however, the gastric secretion is estimated in terms of quantity rather than of acid concentration, it is seen that the denervation is not without effect, for the volume of juice secreted per unit period of time is greatly reduced. In one case the rate of secretion was reduced after operation to about a quarter of its previous level. From this it would appear that the effect of denervation is to reduce the secretion of all the constituents of the juice, the alkaline mucosa and enzymes on their relative concentration. In this respect the effect of denervation is exactly what obtains when the parasympathetic nerve endings are paralysed by atropine.

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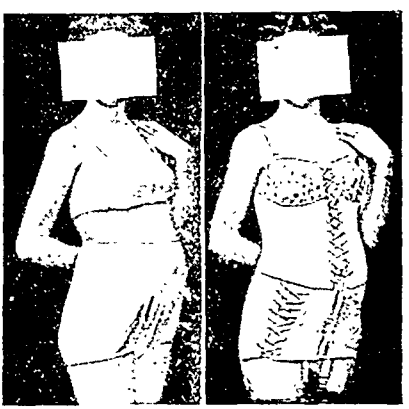

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In addition to its action upon the gastric motility and secretion, denervation has an impressive effect in virtue of division of the pain-carrying nerve fibres. All the four patients subjected to this procedure had been chosen because of the continuance of severe pain despite careful medical treatment; all were emphatic as to the complete relief of pain immediately following operation. It is of course true that similar relief from ulcer pain follows other types of operation, but in these cases I gained the impression that the relief was quite exceptional in its completeness. As an example I quote Case 4. This was a man aged thirty-eight who had suffered from periodic indigestion for about twelve years. During the past year it had been severe and unremitting. He had been in hospital for four months, and during the first eight weeks of that time had been confined to bed and on a rigorous diet with thorough medication, but without relief to the pain—which was severe and incapacitating. At operation there was a gastric ulcer near the lesser curvature, 1 cm. across, and a small active ulcer on the anterior duodenal wall close to the pylorus. By denervation his pain was completely relieved, for the first time for nine months. This observation may be of interest in regard to the general problem of pain in ulcer, for it shows clearly that the pain is visceral in origin, and transmitted by fibres which accompany the antonomic nerves. It appears also to indicate that the pain is not due to increased acidity, as has sometimes been supposed, but is due to increased motility and muscular spasm.

Thus we may conclude that division of the extrinsic nerves of the stomach has an effect upon the gastric motility and its secretion and also interrupts pain sensation. How long these effects will persist, remains to be seen. Resection of autonomic nerves in other parts of the body is notoriously liable to be shortlived in its effects, and a long time must elapse before we can assess the permanency of the functional changes. Similarly a long time must elapse before we can assess the effect of the operation on the healing of the ulcer. The history of the surgical treatment of ulcer is a succession of claims for new operations on the basis of a few cases followed for too short a time, and I make no claim in respect of this operation of denervation. At the present time it must be regarded merely as an interesting experimental observation.

In conclusion, may I emphasise the need for renewed efforts to solve the problem of peptic ulcer. Our present methods of treatment are far from adequate and leave no room for complacency. A great deal of research is called for, not only on those aspects of the gastric physiology to which I have referred, but on others which may be equally important. At present we know little about the secretion of pepsin. It may be much more important than the hydrochloric acid, but owing to technical difficulties in its estimation very few observations have been made on it. We know little about the so-called chemical phase of secretion, which may be due to a hormone produced in the

pyloric segment. We know little also about two other hormones—enterogastrone, which is said to be formed in the small intestine, and urogastrone, which has been isolated from the urine. These hormones are believed to be capable of inhibiting the gastric secretion, and may well prove to be of value as therapeutic agents. All these and many other problems await solution.

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TOMOGRAPHY *

By J. B. McDOUGALL, *C.B.E.*, M.D., F.R.C.P.Ed., F.R.S.Ed.

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ALMOST every organ of the body has been brought within the scope of the radiologist. The advances which have been made in the reproduction of even the finest detail in soft tissues are eloquent testimony to the success of workers in this field. The particular problem of the chest, however, has always been of some difficulty owing to the presence of the bony structures forming the thoracic cage, and it was as a contribution to the solution of this problem that tomography—that is, the reproduction of the chest in layers—was devised.

In radiology it is well known that there may occur a diminution in the translucency of normal lung tissue by reason of thick scapulæ, pectorial muscles, the mammary gland in females or a large thymus gland in children. More important than any of these factors, however, is the presence of the ribs, the shadows of which cover about two-thirds of the lungs. Thus we have a translucent organ, the lung, encircled by much less translucent parts. Not only do difficulties of superimposition arise, but for adequate penetration harder rays must be used than those which would be suitable for the lungs themselves.

Further difficulties in the interpretation of the ordinary antero-posterior films of the chest are due to the superimposition of the structures within the lung itself. Shadows of blood vessels, thickened bronchioles and alveoli are superimposed, and give rise to sharp contrasts which may be wrongly interpreted as being due to pathological lesions. When one recalls that the usual flat film of the chest is simply a product of the shadows of all structures which lie within the effective cone of the rays during the exposure, it becomes evident that the analysis and the interpretation of the final picture may often be difficult and in some cases even misleading.

Stereoscopy as an aid towards the elucidation of intrapulmonary lesions has been given some prominence in recent years. We will readily admit that by the use of the oblique film or the stereoscopic film the expert radiologist is often able to obtain a greater degree of differentiation than is possible with the antero-posterior picture, but, even so, free and isolated vision of different foci is only produced to a limited degree. Furthermore, the fact that a large number of people cannot see stereoscopically limits its practical value and militates against its wide application. The fact has to be recognised that,

* Delivered at a meeting of the Tuberculosis Society of Scotland, held in Edinburgh on 31st March 1944.

despite many attempts to stimulate and maintain interest in stereoscopic work, this method has never been widely adopted, and it is our personal experience that tomography reveals with clarity lesions which are difficult to demonstrate by other methods.

Apparatus.—The fundamental idea of photographing sections of the body as introduced by Bocage is to co-ordinate the motion of the tube and film round an object which remains fixed during the exposure. Objects on a particular plane which is in focus are thus constantly

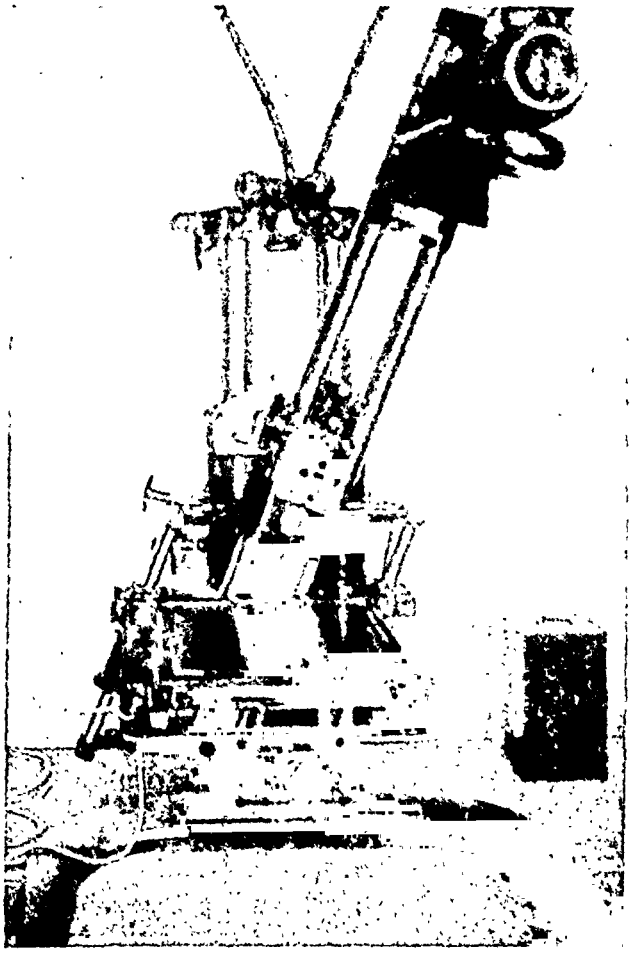

FIG. 1.—The Tomograph.

projected on the same point of the film, while objects lying in any other plane not in focus throw their shadows on different points of the film; as a result of this continuous movement or "wandering" an effacement of the shadows is produced. In the modern tomographic apparatus constructed in 1935 to the plans of Grossman and Chaoul of the X-ray Department of the Charité University Clinic of Berlin, the motion of the tube has been considerably simplified and the use of a diaphragm made possible. Figure 1 is a photograph of the apparatus showing the tube in the initial position of the pendulum. This machine, as manufactured by the Sanitas Electrical Company,

Berlin, and as used by us, consists essentially of a two-armed pendulum oscillating about a horizontal axis. To the upper and longer arm which is above the table is attached a supporting lever for the tube. To the lower and shorter arm, below the table, is attached a rectangular holder which contains the Potter-Bucky diaphragm and the film holder. The tube container may be moved both vertically and horizontally. The difficulties with the diaphragm in the early types of apparatus are avoided by moving the tube in a plane perpendicular to the layer to be photographed. This is achieved by arranging that the plane of the middle-grid element coincides with the plane in which the focus is moved. The pendulum itself is fixed to a block which is suspended between a stand of two posts in such a way that the block can be moved up and down and fixed in any desired position. Above the tube and attached to it is a pulley system running on an arc. The fixation block contains a graduated scale by means of which the extent of the swing of the tube is controlled. The pendulum is pulled over to the initial position at one end of the arc by releasing a pin in the central block.

Technique.—In the examination of a patient tomographic investigation should be used only after having completed the routine radiological examination by means of screening and the usual X-ray photograph. The depth of the patient's chest is measured, and calculations are made for the sections of the chest required. It is at once apparent that the number of sections which can be produced is limited only by the depth of the patient's chest. Then the question has to be settled, not least from the point of view of economy and the time at one's disposal, as to the number of tomograms to be taken in order to provide adequate diagnostic information. Following the practice of Chaoul we take three photographs as a routine in each case :—

1. Ventral ; that is, about 7 cms. from the front of the chest wall.
2. Median ; that is, about midway between the front and the back ; this usually corresponds approximately to the level of the hilum of the lung.
3. Dorsal ; this is, about 7 cms. from the back.

Should the condition of the lung be such that it is advisable to take further sections, it is our practice to take premedian, predorsal and postdorsal photographs at depths of 2 cms. in front of or behind the corresponding main sections enumerated above. It is only rarely, however, that as many sections as this have to be taken to establish the site and distribution of the lesion.

The distances required for the three standard sections having been obtained, the tube is adjusted to the required height and then swung over to the initial position at one end of the arc. The cassette is placed in the position on the film holder, the diaphragm is set and the machine is then ready to take the required photograph.

The positioning of the patient varies in accordance with the photograph to be taken. For an ordinary frontal cross-section of the chest the tube should be moved in a direction parallel to the body axis; thus the patient lies in the long axis of the table. In the case of the other sections, the direction of the tube must be transverse to the body; this is achieved by having the patient lying across the table. The importance of this lies in the fact, as pointed out by Grossman, that the tomograph gives blurring in one direction and, to overcome this, it is necessary to move the tube in a direction perpendicular to the direction of the shadows. This requirement is satisfied by adjusting the position of the patient in the manner just described.

Exposure time is usually one second for taking section photographs. This may appear to be a long period, but experience has shown that it is with this time of exposure that the optimum results are obtained. The voltage and strength of the current are varied for the different

FIG. 1.—Case 1. An anteroposterior picture showing extensive bilateral lesion in a young adult male. (Direct film.)

FIG. 2.—Case 1. A median section of the same chest showing the disease with one or two examples of bronchi and cross-section.

FIG. 3.—Case 1. A dorsal picture showing the extensive cavity formation which is present, but which does not come into view until the dorsal section is reached.

FIG. 4.—Case 2. Large, left upper lobe cavity with fluid level is seen with a smaller excavation directly underneath. (Direct film.)

FIG. 5.—Case 2. A dorsal photograph of the same case taken 7 cms. from the back of the chest and showing the excavation in the left upper lobe, but the lower cavity is not observed.

FIG. 6.—Case 2. A lateral tomogram of the same case showing the two cavities contiguous to each other. The cavity is now brought clearly into view and it is situated in the most posterior part of the chest, that is, about 2 cms. from the transverse process.

sections of the film. For ordinary frontal sections a 6 kilo-watt tube is ample, but for lateral sections a 10 kilo-watt tube is necessary. The optimum voltage and current of the frontal sections is 60 to 65 k.v. with 70 to 110 m.a., working at a distance of 0·9 to 1·5 metres between the section and the film. For lateral photographs, voltages between 80 to 90 k.v. are used with a current of 150 m.a., the time of exposure being the same. Voltage and strength of current may be altered in different cases according to the thickness of the patient and the density of the lesions.

In the apparatus of Bocage the stratum of the body which was photographed was extremely thin, and was really of little value from the point of view of diagnosis. Chaoul has modified this in the apparatus just described. As a result, a stratum of any desired thickness may be reproduced. Actually, the thickness of the cross-section varies with the extent of the arc described by the tube—the greater the arc the thinner is the layer and the smaller the arc the thicker is

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

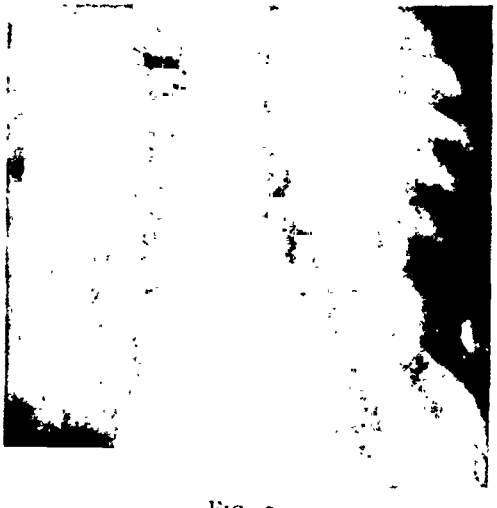

FIG. 9.

FIG. 7.—Case 3. Anteroposterior photograph of a female chest showing a bilateral artificial pneumothorax which was attempted for recurrent small haemoptyses. No benefit resulted from this collapse and the case was sent for further investigation with special reference to the large circular area in the neighbourhood of the left hilum. (*Direct film.*)

FIG. 8.—Case 3. A median section of the same chest showing the outlines of the collapsed lungs with a peculiar folding of the left lower zone, but with no mass yet to be seen in the suspected area.

FIG. 9.—Case 3. A postdorsal section of the same case showing a large mass 6 cms. from the posterior aspect of the chest with a shadow in its centre. This was investigated by the late Mr Laurence O'Shaughnessy by thoroscope. He found a large plum-shaped slightly movable mass in the posterior or mediastinum free from the lung substance, but adherent to both mediastinum and bronchi.

the layer—so that when the arc is at its minimum—that is, nil—and the tube does not swing at all but remains at rest, the section then reproduced comprises the entire thickness of the chest and is really not a section at all; that is to say, the tomograph apparatus is then being used as an ordinary radiographic machine and thus takes the usual X-ray photograph of the chest.

(The lecturer then showed a number of cases of pulmonary tuberculosis which had presented interesting problems, and reproductions of some of the radiograms shown are appended to this article.)

The Scope of Tomography.—If I have limited the description and discussion of results of tomographic investigation to cases of pulmonary tuberculosis it is because as yet our experience of this adjunct to the diagnosis of other conditions is scarcely wide enough to warrant a description of results and to enable us to come to any decision upon its value in such conditions. We have had under investigation cases of Hodgkin's disease, intrapulmonary cysts and lung abscesses, but the field of cranial tomography has not been touched by us, and in the opinion of Chaoul this is a particularly valuable field for investigation. There are also possibilities in the direction of tomography of the heart which still remain to be explored, but clearly many modifications in technique will have to be elaborated before this particular organ can be demonstrated in recognisable sections. Despite the possibilities of tomography in a whole variety of conditions, it is our opinion that its greatest value at the moment lies in pulmonary tuberculosis, which manifests itself in such diverse ways that, even with every method at our command, the problem of diagnosis is at times very difficult.

I have no desire to make any exaggerated claims for tomography, and the indiscriminate use of the apparatus in all cases is certainly to be deprecated. As I have already made clear, tomographic investigation should only be used after routine radiological and screening examinations have been completed; it is then problems calling for elucidation may arise, and that tomography may be utilised as an additional aid. It is felt, however, that the cases which I have described support the opinion that in tomography we have a valuable adjunct to the diagnosis and interpretation of pulmonary lesions and an addition to the armamentarium of the physician and surgeon which one cannot afford to neglect.

THE CLINICAL VALUE OF THE BLOOD SEDIMENTATION DIAGRAM

A Preliminary Report

By HENRYK DLUGOSZ, M.D., Lwów

In medical papers we find discussions as to what the blood sedimentation test should be, and what it is not, rather than observations as to what the blood sedimentation test really is and means.

Although over 2000 papers on the subject of blood sedimentation (BS) have been published, many particulars of it are still unknown, and the clinical value of the BS test is not yet established.

Having carried out 4500 tests of BS during a period of over three years in Polish Military Hospitals in Scotland, I wish to write my observations about the value of the BS test and the BS diagram especially.

Method

The great number of the methods has led to some confusion. Westergren's method, that I have used, is the one most frequently adopted on the Continent and in America. The test is carried out as follows: 0·4 c.c. of the 3·8 per cent. sod. citrate with 1·6 c.c. of the venous blood, set vertically in tubes of 2-3 mm. of diameter, 200 mm. high, in normal room temperature, not in sunshine, nor near a fireplace or central heating pipes.

In Westergren's method the results of sedimentation are usually determined by millimetres in the first hour, seldom after 2 hours and very rarely after 24 hours. After some preliminary tests as above I introduced the long observation, and noted the results in millimetres after ½, 1, 1½, 2, 3, 4, 6, 10, or 12, 22 or 24 hours.

At first I noted the results myself, then I made use of the observation of my intelligent patients, who did not know the examined persons' names.

Marking the figures of sedimentation on the vertical and those of the time on the horizontal, some points between the co-ordinates are found. The junction of all points with a line gives the BS diagram during periods of 22 and 24 hours respectively.

The BS Diagrams

The BS diagrams are not new. Westergren, Plaut, Kok, Gueissaz, Peschel, Raykowski, J. Cutler and many others used diagrams, but the time of their observations of BS was short, ½-4 hours, and they employed many different methods.

My idea is to use Westergren's method and note the results from ½ to 22-24 hours, as mentioned above. The diagram that I suggest making does not take up so much time as might appear at first sight. A carefully taken detailed history or careful physical examination or many laboratory tests take up a lot of time, too, and it is not " wasted time."

The Norm

The BS diagram of healthy people is shaped like a highly elongated printed letter " S." From my experience the maximum figures of a normal diagram are as follows : in the first hour 5 mm., after two hours 10, after three 15, after four 20, after six 26, after ten 36, after twelve 41, after twenty-two 55, after twenty-four hours 56 mm. Corresponding minimum figures are : 2, 6, 10, 14, 20, 30, 33, 40, 41 mm. (Chart 1).

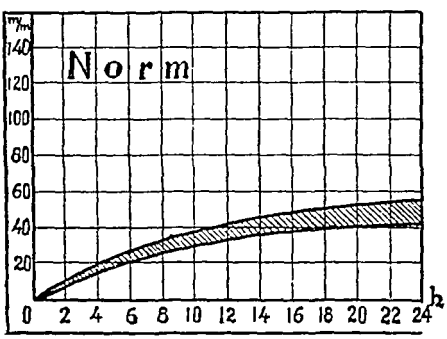

Chart 1.—Norm.

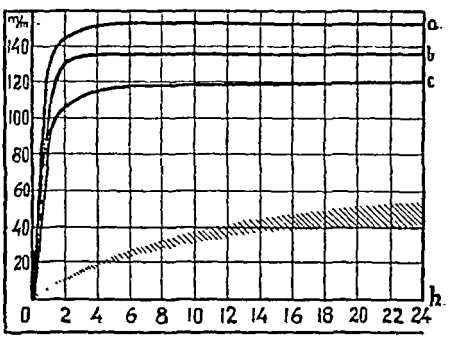

Chart 2.—Acute Inflammation.

Diagrams above maximum figures mean accelerated, and below minimum figures mean delayed, sedimentation. Both are always pathological. In this connection it must be remarked that the cause of accelerated sedimentation is easier to determine clinically than that of delayed sedimentation.

Importance for Diagnosis

The BS diagram has an importance for the diagnosis of the state of the patient, especially if the clinical symptoms and signs are insignificant or if they are only symptoms and the physician is asked about the state of health of the patient.

Some examples

Case 1.—The patient complained of general weakness, shortness of breath, palpitation on walking. Fever 100° F., pulse 104 per minute. Physical signs of mitral incompetence and stenosis, bronchitis, liver and spleen enlarged, slight œdema of the feet. The physical signs were not alarming, but BS diagram showed clearly the gravity of the state (Chart 2 (*a*)). Later on there were exacerbations of endocarditis with cardiac failure. The patient was discharged slightly improved, but unfit for duty.

CASE 2.—The patient had acute tonsillitis and pains in knee and elbow joints. Seven days later no fever, but general weakness and shortness of breath on exertion remained. On examination two weeks after the first symptoms of tonsillitis: temperature normal, pulse 84 per minute, rhythmic. No physical signs of heart disease. Joints not swollen, elbow and knee joints painful on movement. In contrast with the minimum physical signs the BS diagram did not show normal conditions (Chart 2 (*b*)). Then the electrocardiogram: partial a-v block with P-Q 0·24 sec. Later physical signs of endocarditis of mitral valve. The patient was discharged in a good condition, fit for auxiliary service.

CASE 3.—The patient complained of severe pain in both knee joints. Ten years ago acute rheumatic arthritis. On examination: temperature normal, the knee joints slightly swollen and painful on movement. No changes in internal organs, especially in the heart. Discrepancy between the complaints and physical signs was explained by the BS diagram, which pointed to inflammation (Chart 2 (*c*)). The patient was still undergoing treatment at the time of writing.

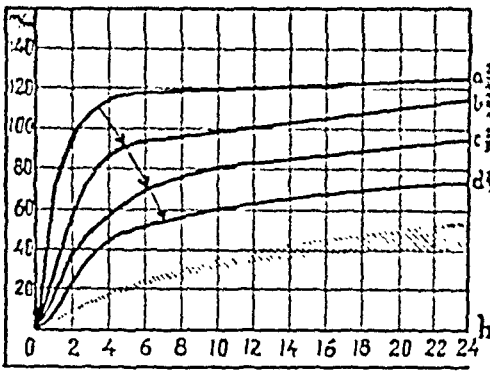

CHART 3.—Acute Myocarditis.

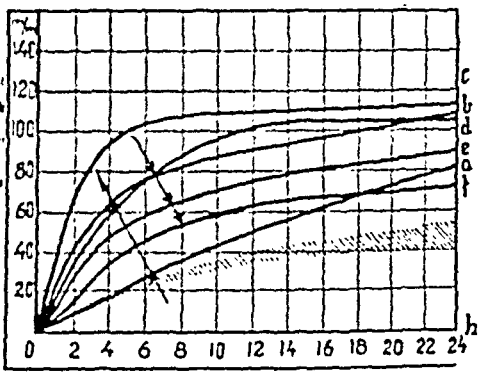

CHART 4.—Tuberculous Pleurisy.

CASE 4.—The patient complained of general weakness, dyspnœa and palpitation on exertion. Five days ago acute tonsillitis with fever 104° F., lasting three days. On fourth day collapse after a walk. Therefore sent to hospital. On examination on fifth day of the disease: temperature normal, pulse 84 per minute, traces of tonsillitis. No heart changes physically. Liver and spleen not enlarged. Joints normal. It was necessary to reach a decision: fit or unfit. The BS diagram indicated immediately the presence of the disease (Chart 3 (*a*)). Tonsillectomy and heart treatment. After three months fit for duty.

The above-mentioned BS diagrams show clearly the deviation from the norm. Acute inflammations, particularly due to rheumatic arthritis, cause the greatest acceleration of the sedimentation during the first hour and a slight one only in the following hours, so that the BS diagram is shaped like the hands of a clock at 6.15 (Chart 2 (*a*), (*b*), (*c*); 3 (*a*)).

Chronic inflammations cause a considerable BS acceleration in the first hour, but also and more particularly in the second hour. The BS diagram is shaped like the hands of a clock at 7.12 (Chart 3 (*b*), (*c*)).

More chronic inflammations produce BS acceleration in the first hour, but more in the second and more particularly in the third hour (Chart 3 (*d*)).

From the above it is evident that the indication of blood sedimentation in the first hour is different from the second and following hours. To take the results of the first hour only or of the first and second, added and divided by two and so on, gives no proper result. In the early period of tuberculosis exacerbation, the first days of pleurisy, the BS diagram may be normal during the first six hours, and then is distinctly above norm (Chart 4 (*a*)). Therefore the observation of the BS must be longer than one or two hours to avoid a discrepancy between the BS and the clinical state.

The figures of the BS above norm in later hours are, I suppose, characteristic of the early stage of the exacerbation of tuberculosis.

From all the above-mentioned examples it is clear that the BS diagram made over longer periods shows the condition of the patients better than the figures for the first hour. A glance at the BS diagrams facilitates the diagnosis of the acute or chronic stage of the disease, which is so important for observation of the course and prognosis, and may be very important for a decision regarding the time of fitness.

BS Diagrams in Cases of Anæmia

It is assumed by many authors (Naegeli, Wintrobe, Frimberger and others) that the BS rate is parallel to the degree of anæmia, and that the results should be corrected on this hypothesis. Basing my

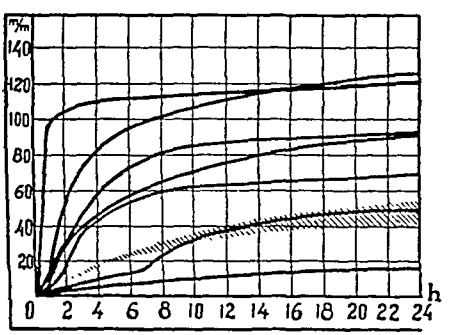

Chart 5.—Anæmias. R.B.C. all 4·0-4·1 mill.

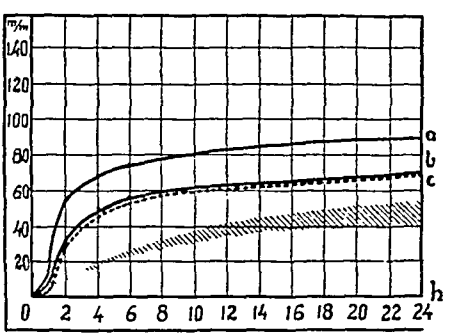

Chart 6.—Late Syphilis.

conclusion on 112 cases of anæmia of different types and degrees, I deduce that the BS diagram is parallel to the degree of anæmia only in anæmias due to hæmorrhage and in pernicious anæmia. In other types of anæmia due to hæmoglobinuria paroxysmalis, malaria, ankylostomiasis, trichuris trichiura and some hypochromic anæmias in women, there is no correlation between the BS diagram and the degree of anæmia.

Chart 5 shows the BS diagrams of 7 patients with 4·0 to 4·1 mill. red blood cells per cubic millimetre. The patients all showed the same degree of anæmia, but in spite of that there was great variety

in the diagrams. In severe anæmias, especially those due to ankylostomiasis, the BS diagram is normal during 24 hours of the observation. This fact may be useful in the diagnosis of the type of hypochromic anæmias, but not in the determination of the degree of anæmia.

In other words, accelerated sedimentation does not indicate anæmia, and normal or even delayed sedimentation does not exclude it. The correction of the BS results by the degree of anæmia is meaningless.

BS Diagrams in Late Syphilis

The BS diagrams have led me often to the discovery of syphilis, the presence of which was not suspected by the patients, or by the doctors who had examined them because of the lack of history of syphilis and often of clinical signs. In late syphilis, and very often in hepatitis in syphilitic persons, the BS diagrams differ from norm and from the types above mentioned. In the first hour, sometimes in the second and more rarely in the third hour, the BS diagram is normal, but then in half an hour the red corpuscles start suddenly to subside very quickly and the result is a bayonet-like diagram.

Some Examples

Case 5.—The patient complained of progressive wasting and weakness, physical signs of bronchitis. Chest X-ray examination normal. The BS diagram (Chart 6 (*a*)) very strange: in the first hour sedimentation almost normal, after one and a half hours red cells started suddenly to subside very quickly, producing the bayonet-like diagram. At first I thought of some technical fault. I repeated the test, and I was surprised when three days and again one month later the BS diagrams were like the first one. In anamnesis no syphilitic infection. Both Wassermann and Kahn tests strongly positive. Specific treatment. Recovery.

Case 6.—The patient, who had always been healthy, complained of headache and great irritability. He has been in constant trouble with his chiefs. No physical signs of the disease. The BS diagram bayonet-like again (Chart 6 (*b*)). Both Wassermann and Kahn tests strongly positive. Specific treatment. Recovery. Now very busy and happy in the Polish Merchant Navy.

Case 7.—The patient complained of progressive weakness, poor appetite, epigastric discomfort after meals and pyrosis. On examination: the pupils unequal. No Argyll Robertson's sign. X-ray examination of digestive tract did not reveal any changes. The BS diagram bayonet-like (Chart 6 (*c*)). Both Wassermann and Kahn tests positive. The patient is still undergoing specific treatment.

Case 8.—The patient was sent to the hospital because of jaundice due to abuse of alcohol. The first antisyphilitic treatment three months before the admission. On examination: blue line on the margin of the gum. Liver and spleen enlarged. The BS diagram bayonet-like (Chart 7 (*a*)). With improvement the red blood cells started to subside quickly rather later (Chart 7 (*b*) with relapse earlier (Chart 7 (*c*)) with recovery later again (Chart 7 (*d*)).

I would suggest that this sign may be helpful for the observation of liver

function during specific treatment. Chart 8 (*a*) shows schematic recovery, 8 (*b*) relapse.

CASE 9.—The patient, always healthy before, complained of headache and progressive weakness. No syphilitic infection in anamnesis. On examination: the pupils unequal. Argyll Robertson's sign, knee reflexes normal. The

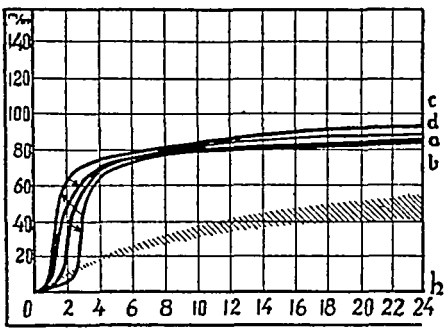

CHART 7.—Syphilitic Hepatitis.

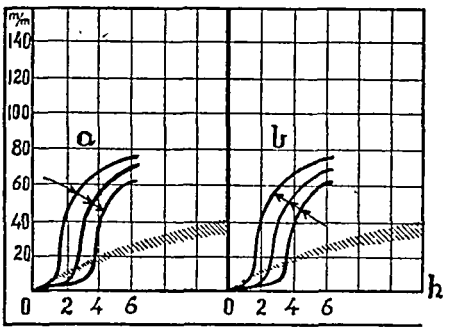

CHART 8.—Hepatitis (*a*) recovery (*b*) relapse.

BS diagram as in chronic inflammation (Chart 9 (*a*)), but careful physical and X-ray examination did not reveal any changes. Both Wassermann and Kahn tests strongly positive. Specific treatment. Improvement.

CASE 10.—The patient, suffering from iritis, complained of mental depression. Always healthy before admission. On examination: hypochromic anæmia. Physical examination and laboratory tests did not reveal cause of anæmia. The BS accelerated, but not in the first hour (Chart 9 (*b*)). Both Wassermann and Kahn tests strongly positive. Specific treatment. Recovery.

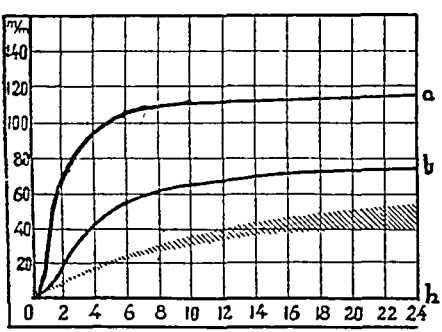

CHART 9.—Late Syphilis.

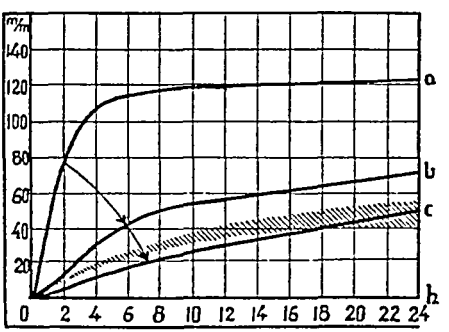

CHART 10.—Pulmonary Infarct,

Bayonet-like BS diagrams show most evidently that the first hour's and very often the second hour's result, or even the figures obtained by means of numerous formulas, co-efficients and logarithsms of the first and second hours, cannot give the real course of BS or the real condition of the patient.

I suggest as a practical conclusion: if BS is accelerated without the presence of significant symptoms or signs of the disease, especially if the BS diagram is bayonet-like, the Wassermann reaction should be tested. On the other hand, the normal BS diagram does not exclude syphilis.

Importance during the Clinical Course

The BS diagram is constant during weeks, months and years, if the condition of the examined person does not change. Therefore the BS diagram may be used as a very important test for the observation of the course of the disease. A number of BS diagrams, made over proper intervals of time, perfectly represent the condition of the patient, namely the increase of the symptoms, the maintenance of the state at the same level, the improvement and the recovery or complication, or finally the relapses. There is a close parallelism between BS diagrams and the condition of the patients. The data obtained from a frequent charting of BS diagrams are superior to those obtained by any other single procedure. Besides the examples already shown in Charts 3, 4, 7, I give, owing to the shortage of paper, only three more examples.

Case 11.—After gastro-entero-anastomosis because of duodenal ulcer there was infarction of the lung. The condition was grave during the first seven days. The BS diagram (Chart 10 (*a*)) is like the position of the hands of a clock at 6.15. Parallel to the improvement the BS diagram nears the norm (Chart 10 (*b*)). In good conditions BS diagram is normal (Chart 10 (*c*)).

Case 12.—Patient with creeping pneumonia. The condition of the patient very grave. The BS diagram is like one produced by acute inflammation (Chart 11 (*a*)). During the next four weeks the BS diagrams (Chart 11 (*b*) (*c*)), like the first, in spite of short periods free from fever. Later the BS diagram (Chart 11 (*d*)) is like the position of the hands of a clock at 7.12, when the patient's condition was rather improved. At last, on recovery, the BS diagram was normal (Chart 11 (*e*)).

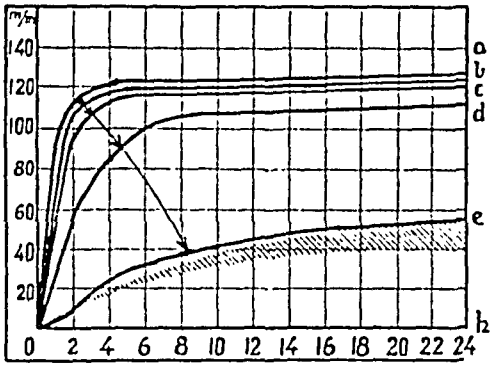

Chart 11.—Creeping Pneumonia.

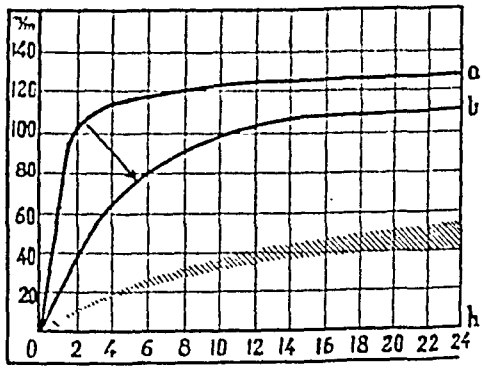

Chart 12.—Fibrocavernous Tuberculosis.

Case 13.—The patient with chronic pulmonary tuberculosis (fibrous cavity). Temperature 100° F. Tubercle bacilli in sputum. General condition very poor. The BS diagram (Chart 12 (*a*)) is like the position of the hands of a clock at 6.15. After 11 days' rest, dietetic treatment and calcium injections improvement: temperature normal, good appetite, increase of weight. The second BS diagram in this time (Chart 12 (*b*)) resembles the position of the hands of a clock at 8.15. The diagram " (*b*) " is at the beginning much lower than the diagram " (*a*) " and almost on the same level at the end, because the patient's condition had improved, but anatomic changes remained the same.

The BS diagram 12 (*b*) shows clearly that the observation of BS must be longer than one hour to avoid a discrepancy between the BS diagram and the state of the patient.

Delayed BS

Delayed BS was observed in about 5 per cent. of cases, excluding cases of delayed BS due to jaundice and heart failure.

About 30 per cent. of the patients with delayed BS present a distinctive pattern, which is characterised by the exhaustion of the vitality of the nervous system. The patients are depressed, tired, despondent, they have a poor appetite, and they lose weight. On examination: the palms wet, vasomotor disturbances of the skin, very often gastro-enteroptosis (X-ray). No visible cause of the illness.

The rest of the patients with delayed BS show diseases caused by giardia, strongyloides stercoralis, tænia solium, dibothriocephalus latus, and diseases such as: urticaria, bronchial asthma, paroxysmal hæmoglobinuria, very often duodenal ulcer without complications. Delayed BS indicates an allergic state. Many of those patients have been improved after treatment with vitamins A, D, C.

The BS Test as an Index to Condition

Neither an accelerated nor a delayed BS test serves to diagnose the entity of the disease, but only indicates the pathological condition of the person examined. The BS diagrams are the same in many different diseases if the condition of the patients is the same, and may be different in one disease if the condition of the patient changes, because the BS test is a test of the state, of the condition of the patient, and not a test of this or that disease.

As regards normal BS diagrams there is much confusion. It is true that healthy people have a normal BS diagram, but a normal BS diagram does not necessarily mean that the person examined is healthy. I observed, for example, three patients in good condition, without fever, but with fibrocavernous tuberculosis, with tubercle bacilli in sputum and their BS diagrams, many times made, were always normal. Therefore the BS diagram, if normal, is useless in mass examination for social anti-tubercular action. This, however, cannot be used as an argument against BS tests or BS diagrams as such.

Different Methods

If I wrote that Westergren's method, most often used on the Continent and in America, is the best, I did not mean to suggest that other methods are not good. For practical purposes many methods can be used, but each one must have its own "norm," and the observation must be long enough. On the other hand, if we doctors want to understand each other and compare our results with those of others,

we must use one method. It is impossible to convert the results of one method into those of another.

The results of a BS test will be more satisfactory and most useful for clinical purposes if in the form of 22 or 24 hours BS diagrams, because they best illustrate the complex phenomenon of red blood sedimentation.

SUMMARY

The author suggests that the best plan is to use Westergren's method and to note the results in millimetres after $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, 4, 6, 10 or 12, 22 or 24 hours in order to obtain BS diagrams during periods of 22 and 24 hours respectively.

The BS diagram is very useful for the diagnosis of the condition of the patient, especially if the clinical signs are insignificant.

Acute inflammations cause the greatest acceleration of BS during the first hour and a slight one only in the following hours.

Chronic inflammations cause considerable BS acceleration in the first hour, but also and more particularly in the second hour.

More chronic inflammations produce BS acceleration in the first hour, but more in the second and more particularly in the third hour.

In the early period of tuberculosis exacerbation the BS diagram may be normal during the first six hours, but then is distinctly above norm.

The BS diagram is parallel to the degree of anæmia only in anæmias due to hæmorrhage and in pernicious anæmia, in other types of anæmia there is no correlation between the BS diagram and the degree of anæmia. The corrections of the BS in anæmias are meaningless.

In late syphilis the BS diagram is bayonet-like, or very distinctly above norm.

BS diagrams are very important for the observation of the clinical course of diseases, because there is a close parallelism between the BS diagrams and the condition of the patients. BS diagrams during the period of 22 or 24 hours are most satisfactory and most useful for clinical purposes.

I wish to express my thanks to all those fellow-doctors who have helped me with this work, especially to Dr E. Stefek and Dr I. Spitzer.

My thanks are due to Miss Isobel May, Ph.D., for the linguistic revision of the paper.

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PERISCOPE

A NEW TEST FOR CHRONIC PANCREATITIS

The authors report experiments undertaken to find a satisfactory test for pancreatic function by stimulation of the organ with mecholyl and secretin. The experiments were carried out in dogs. By injecting secretin alone it is possible to employ a dose which will raise the level of the enzymes, amylase and lipase in the serum in pancreatic obstruction and not when the pancreas is normal. Greater stimulation can be obtained by the use of mecholyl and secretin. After finding the amount of these drugs which would regularly produce an increase of serum lipase thirty to sixty minutes after injection, the authors tested the effect of similar doses on dogs in which the pancreatic ducts had been obstructed. If ligature of the ducts had resulted in only slight induration of the pancreas a normal response followed injection of the drugs, but if atrophy and cirrhosis of the pancreas had occurred no increase in blood enzymes took place. The results obtained were more consistent than those reported for the use of mecholyl and eserine. The authors suggest that the new test should give significant information and might be successful in human cases of pancreatic disease.

H. L. POPPER, M.D., *et al.* in *Surg. Gynec. and Obst.* (1943), 11, 471.

SULPHONAMIDES IN BRONCHIAL SECRETION

The distribution of orally administered sulphonamides amongst the various body fluids has already been thoroughly worked out, but little attention has been paid to their effect on the bronchial secretion. The frequency of bronchial infection would seem to justify an investigation of the possible action of these drugs in this type of disease. In order to do this, the author studied 12 cases of acquired bronchiectasis from which bronchial secretion was obtained by bronchoscopy every few days. Sulphadiazine was given by mouth in sufficient dosage to maintain adequate blood levels of the drug. These values ranged from 3·9 mg. to 16·4 mg. per 100 c.c. of blood, and at the same time the concentration of sulphadiazine in the bronchial secretion varied from 1·8 to 11·6 mg. per 100 c.c. This gives an average ratio between the two concentrations of 0·58. In other words, the bronchial fluids contained rather more than half as much sulphadiazine as was present in the blood.

As an adjuvant measure to improve bronchial drainage, bronchoscopic aspiration was performed at intervals of two to four days during the time the drug was being taken by the mouth. There was little effect on the character of the bronchial flora but the odour was considerably modified. In every case the combined treatment resulted in a very definite decrease in the amount of sputum, the actual reduction varying from 55 to 81 per cent. with an average of 69 per cent. Sulphadiazine instilled into the bronchi disappeared rather rapidly, and this method was less useful than oral administration.

C. M. NORRIS, M.D., in *Journ. Amer. Med. Assoc.* (1943), 123, 667.

NEW BOOKS

Supplement to the Extra Pharmacopœia (MARTINDALE). Pp. 48. London: The Pharmaceutical Press. 1944. Price 2s.

Martindale's well-known *Extra Pharmacopœia* is now issued by the Council of the Pharmaceutical Society.

Since the appearance of the Twenty-second Edition in 1941, many changes have been made in the B.P. and the B.P.C., chiefly arising from war conditions. This small book has been issued to bring it up to date.

It gives details of the principal changes that have been made in the fourth, fifth and sixth addenda to the B.P. and to the recent supplements to the B.P.C. A list of the preparations included in the National War Formulary is given, and recent changes in the U.S.P. are noted. There is also a section which summarises the recent orders affecting the supply of drugs.

Those who rely on " Martindale " will welcome the additional information included in this little book.

Practical Anæsthetics. By J. ROSS MACKENZIE, M.D., D.A. (ENG.). Pp. viii+136, with 63 Illustrations. London: Baillière, Tindall & Cox. 1944. Price 10s. 6d. net.

Within a very limited compass the author has contrived successfully to cover all aspects of practical anæsthetics including inhalational and intravenous anæsthesia and local and regional analgesia. Only a teacher with the wide experience of Dr Mackenzie could have produced such a concise yet comprehensive guide to the essentials of the subject and maintained correct accentuation of major features. The free use of tabulated summaries will be particularly useful to examination candidates during revision.

The illustrations are relatively plentiful and well chosen and the general production is attractive.

Diseases of the Chest. By ROBERT COOPE, M.D., F.R.C.P. Pp. 524, with 126 illustrations. Edinburgh: E. & S. Livingstone. 1944. Price 25s.

The excellent qualities of Dr Coope's textbook on Diseases of the Chest cannot be gainsaid. The author has not only written a book which will be hailed by students of medicine as a classic but one that will also be most acceptable to practitioners.

Minor criticisms could be offered on such points as his use of the term Psittacosis when probably Ornithosis would seem more accurate. The suggestion that a competent clinical pathologist has a fair chance of finding malignant cells in the sputum of a case of bronchial carcinoma is, to say the least of it, definitely specious. The chapter on pulmonary tuberculosis does not go into very much detail.

Irrespective of these shortcomings the whole book has many fine attributes and must receive its due meed of commendation. The sections dealing with clinical examination and physical signs are particularly well done. The beautifully coloured microphotographs from Dr Robertson Ogilvie's collection are without doubt a valuable asset. The neat little diagrammatic sketches interspersed throughout the text clarify many a fundamental principle in a simple way. A book of this type has been needed for some time and Dr Coope must be congratulated on bringing to his readers first-class material in such an attractive form.

Prevention and Treatment of Diseases of Warm Climates. By T. GERALD GARRY, M.D. Pp. 1-94. London: Medical Publications Ltd. 1944. Price 8s. 6d. net.

This small book the Author, who is senior physician to the Anglo-American Hospital, Cairo, dedicates to the Armed Forces, Everywhere. It is also intended for traders, travellers and others located in isolated districts where medical assistance is unobtainable. It is divided into two parts. The first deals with food, water, exercise and the prevention of disease. In the second a very brief description of the features and treatment of a number of diseases is given. The revision of the proofs has not been very careful; a number of mistakes in spelling occur. There is no index. The book gives some useful advice, particularly in Part I, and it may be found helpful by those for whom it is intended.

The Midwife's Text-Book of the Principles and Practice of Midwifery. By R. W. JOHNSTONE. Pp. vii+365, with 205 illustrations. London: Adam and Charles Black. 1944. Price 18s. net.

This book, written by the Professor of Midwifery at Edinburgh University, who is also the present Chairman of the Central Midwives Board for Scotland, is based on the lectures he has delivered with great acceptance for a considerable period of years to pupil-midwives. Clear, well-written and liberally illustrated by a few beautifully reproduced coloured plates, many diagrams and some X-ray photographs, it builds up step by step, the information, with the underlying reasons and explanations, which the well-educated midwife now requires if she is to play her responsible part in modern obstetrical practice. It is intended to be of use not only during the period of training, but one to which reference can be made by the practising midwife, for it indicates her sphere in the team work now necessary to give the best obstetrical service. Several colleagues have contributed sections on subjects of which they have special knowledge to make the whole an authoritative statement of present-day opinion and practice. A chapter on Midwifery in Relation to Public Health in both England and Scotland should prove of help in orientating the midwife's position and in indicating her opportunities of service in the larger field of Preventive Medicine. The last chapter is devoted to a History of Midwifery in which the reader will find a fascinating story well told.

BOOKS RECEIVED

BELLOWS, JOHN G., M.D., PH.D. Cataract and Anomalies of the Lens. (*Henry Kimpton, London, W.C.* 1) 60s. net.

DIBLE, J. HENRY, M.B., F.R.C.P., and THOMAS B. DAVIE, B.A., M.D., F.R.C.P. Pathology: An Introduction to Medicine and Surgery. Second Edition. (*J. & A. Churchill Ltd., London*) 45s. net.

DODSON, AUSTIN INGRAM, M.D., F.A.C.S. Urological Surgery. (*Henry Kimpton, London, W.C.* 1) 50s. net.

Catalogue of Lewis's Medical, Scientific and Technical Lending Library. Part I.: Authors and Titles . (*H. K. Lewis & Co. Ltd., London*) To subscribers, 12s. 6d. net. Non-subscribers, 25s. net.

LEWIS, Sir THOMAS, C.B.E., F.R.S., M.D., D.S.C., LL.D., F.R.C.P. Exercises in Human Physiology . . (*Macmillan & Co. Ltd., London*) 3s. 6d.

MCDOWALL, R. J. S., M.D., D.SC., M.R.C.P. Handbook of Physiology and Biochemistry (originally "Kirkes" and later "Halliburton's"). Thirty-eighth Edition . . . . . (*John Murray, London*) 25s. net.

THOMAS, E. W. CARYL, M.D., B.SC., D.P.H., Barrister-at-Law. A Synopsis of Forensic Medicine and Toxicology. Second Edition. (*John Wright & Sons Ltd., Bristol*) 10s. net.

WHITING, MAURICE H., O.B.E. Ophthalmic Nursing. Fourth Edition. (*Messrs J. & A. Churchill Ltd., London*) 6s. 6d.

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Edinburgh Medical Journal

May 1945

RECENT DEVELOPMENTS IN THE TREATMENT OF PULMONARY TUBERCULOSIS*

By R. Y. KEERS, M.D., F.R.F.P.S.

Senior Physician and Medical Superintendent, Tor-na-Dee Sanatorium

I HAVE chosen to speak this afternoon on "Recent Developments in the Treatment of Pulmonary Tuberculosis" because the rise in the incidence of this disease which the present world war has brought to us presents the physician with both a problem and a challenge. Of clinical material there is abundance, as the waiting lists of our sanatoria and chest hospitals will bear witness, and the cessation of hostilities will not automatically arrest the ravages of the tubercle bacillus among our people. It seems opportune, therefore, to overhaul our armoury and to consider the modifications and re-adjustments which have been effected in our therapeutic equipment during the past few years.

REST

It is safe to say that there has been no fundamental change in the basic principle which governs the treatment of pulmonary tuberculosis. This principle is rest—mental and physical, local and general. The beneficial effects of rest have long been recognised, and nothing which has transpired within the past decade has in any way upset our belief that a prolonged period of bed-rest is probably the most important single factor in the arrest of the tuberculous process. Indeed the tendency nowadays is for rest to be applied more strictly than ever, and the former general rule that the patient should remain in bed only until the disappearance of fever has been rightly discarded. Instead we now insist upon strict bed-rest (and by that I mean that the patient remains in bed for all purposes) until the temperature has subsided, and then, after it has been normal for a month, the question of permitting one daily visit to the lavatory may be considered. Further steps are governed by the degree of radiological improvement observed, and it is only when evidence of such improvement is definitely established that the patient should be allowed up to wash and bath. He then remains at this stage until the sputum has become negative, the blood sedimentation rate normal

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 8th February 1945.

and the radiological appearances suggest that healing is proceeding satisfactorily. Rigid criteria, certainly, but if we accept the hypothesis that rest is the basis of treatment (and the evidence in support of such hypothesis is conclusive), then there is everything to be gained by adherence to them. The same tendency towards increased insistance on bed-rest is found to-day in America. In March last year, Willis, addressing the Californian Tuberculosis Association, said, " Emphasis is more and more being placed upon placidity of mind and body as essential to early recovery. The patient is being told as never before of the advantages of relaxation."

While modern opinion is unanimous on the advantages of prolonged rest, we are at present unfortunately hindered in its application by the lack of sufficient accommodation to apply it in its full rigour. The bogey of the waiting-list is ever at our heels, forcing us at times to adopt a short-term policy of patching up rather than the complete re-conditioning which the situation really demands. Shortage of accommodation and administrative difficulties may possibly be a valid excuse in war-time, but these should not be allowed to handicap our efforts in the succeeding years.

It must be made clear, however, that the policy of prolonged bed-rest refers only to those patients who are likely to benefit from such treatment. The case with gross fibrosis and cavitation, or who is past middle age, is not likely to make a brilliant response to a long-drawn-out régime of inactivity, and the scheme of treatment should be modified accordingly.

Collapse Therapy

Together with this modern trend towards longer periods of rest, interest in collapse therapy has continued to develop steadily, and much has been learnt in recent years, particularly regarding the application and scope of surgical collapse. The trusty triad, artificial pneumothorax, phrenic paralysis and thoracoplasty, is still the mainstay of the tuberculosis physician, but ideas as to the precise indications for these procedures have altered radically. In addition, new methods of collapse have been explored: extrapleural pneumothorax and closed suction drainage of cavities have come and gone, and now pneumoperitoneum is emerging from its preliminary trials with a reasonable degree of credit. Resection of a lung or lobe of a lung for pulmonary tuberculosis, long considered to be far outwith the bounds of possibility, has been performed, and it seems likely that more work along these lines will be carried out. The sphere of collapse therapy is not a limited one, and a review of modern ideas on the subject will allow us to appreciate its possibilities.

Artificial pneumothorax, introduced by Carlo Forlanini in 1888, is now well known to us all as being far and away the most widely practised method of therapeutic lung collapse in use to-day. It

passed through its trial stage years ago, and has been applied with increasing energy and vigour in every country in the world wherever the nucleus of a tuberculosis service exists. Its individual successes have been numerous, and its efficacy was greatly enhanced by the introduction of the thoracoscope in 1912 by Jacobaeus of Stockholm, in an endeavour to solve one of the great problems associated with this method of treatment—the presence of pleural adhesions. These adhesions, the result of involvement of the overlying pleural layers in the tuberculous process, were encountered in a very high proportion of cases and were naturally located over the diseased area of lung—the very area where the maximum degree of relaxation was desired. Thus in many instances pneumothorax failed in its objective: open cavities were anchored to the chest wall by adhesion bands, infiltrated apices failed to separate from the thoracic dome, and the patient continued to cough up bacilli-laden sputum and to spread his disease slowly but steadily throughout the remaining relatively healthy lung fields. Nor was this failure to collapse the affected portion of lung the only disadvantage associated with pneumothorax. It was found that a high proportion of cases developed effusions in the air-filled pleural space, often associated with fever and much constitutional disturbance; and in some instances this fluid became tuberculous pus—not a very happy state of affairs, particularly when many of these tuberculous empyemata ruptured through the lung, forming broncho-pleural fistulæ followed by secondary infection. The fate of these patients was an unhappy one and the casualty list was high, but pneumothorax maintained its popularity, and in contemplation of its successes its failures tended to be overlooked.

Let us review its position to-day and consider the changing ideas and modifications in technique which the past few years have brought us. The vague sense of dissatisfaction with the general results of this form of treatment, which was gradually making itself felt, was sharply crystallised recently in the Fifty-Eighth Annual Report of the Trudeau Sanatorium by Dr Fred. H. Heise, the Medical Director, who wrote: "One major change in treatment is gradually taking place. Pneumothorax, by some thought to be a substitute for ordinary dietetic-hygienic measures and by many regarded as the long-looked-for cure-all, to a large degree has lost its glamour. Serious complications and an increased death-rate attendant upon its free use have diminished considerably its usefulness. To-day we advise it when we must and desire it less and less." Furthermore, in a recent survey of one hundred American Sanatoria and chest hospitals, Drolet (1943) states that "in isolated instances certain surgical operations achieve remarkable results and save a few lives: too often other collapse measures unfortunately add complications to already serious cases."

Authoritative statements such as these compel attention, and call seriously for a re-assessment of this method of treatment, now used so freely throughout our sanatoria. Both Heise and Drolet have

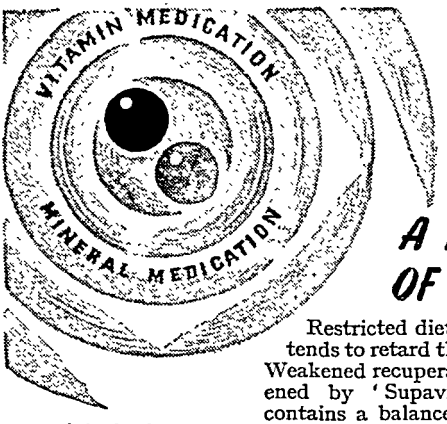
emphasised the disastrous effect of complications—those complications which we have already mentioned, pleural adhesions, effusions and tuberculous empyemata. The effect of pleural adhesions in interfering with efficient collapse of the diseased lung is sufficiently serious in itself, but there is an even blacker side to the picture. It is now well recognised that the incidence of effusion and its serious sequelæ is very much higher in those cases in which adhesions exist and in which they cannot be divided by the thoracoscope and electro-cautery (Michetti, 1938; Keers, 1940; Simmonds, 1941; Hoyle, 1943).

We have, therefore, reached a point in the study of artificial pneumothorax where our big problem is the discovery of a really adequate solution to this question of the adherent pleura. It may perhaps be most readily surveyed by considering first the selection of cases for treatment and later the management of the treatment, particularly during the early months. In selecting cases for pneumothorax it should be remembered that the aim is not only to secure an effective collapse which will result in healing of the tuberculous disease, but that at the conclusion of the treatment the lung should be capable of re-expansion and of function, in so far as formation of scar tissue will permit. If the lung eventually proves incapable of re-expansion there is reasonable ground for supposing that the original choice of therapy had not been the most suitable, and there is no need nowadays to pin all our faith on pneumothorax: the thoracic surgeons have provided suitable alternatives for varying types of case.

Rafferty (1943) has recently made a notable contribution to this aspect of treatment by enumerating a list of definite pulmonary contra-indications to artificial pneumothorax. He points out that disease which is predominantly fibroid, even if unilateral, is not suitable, for here the involvement of the pleura in the pathological process is usually obvious and there is a strong presumption that adhesion formation will prevent an effective collapse. Moreover, the fact that the lung has obviously undergone considerable scarring and contraction means that, even if a pneumothorax is induced and maintained, ultimate re-expansion can only take place at the expense of mediastinal displacement and emphysema of the contralateral lung. In such cases surgery represents a much more effective and less treacherous method of treatment.

The large apical cavity is almost invariably a further contra-indication Adhesions are extensive and usually indivisible, attempts at cauterisation being followed in most instances by severe pleural infection; while again, even if successful collapse is achieved, re-expansion is difficult, and in these cases, too, thoracoplasty is the treatment of choice.

In very recent times one further contra-indication has been added to the list, namely, tuberculous disease of the bronchi complicating the intrapulmonary lesions. It is not yet possible to arrive at any definite estimate of the frequency of tracheo-bronchial tuberculosis,



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but evidence is accumulating that this condition is more common than was originally thought. Involvement of the mucous membrane of the bronchus takes place by direct implantation of bacilli from the lung lesion, and ulceration, granulation tissue formation and cicatrisation may all be found. When cicatrisation is present, resulting in partial bronchial stenosis, induction of a pneumothorax and the consequent reduction in lung volume produce shortening of the bronchus in its long axis and may thus convert a partial narrowing into a complete occlusion of the bronchial lumen. Atelectasis ensues, with stagnation of secretion distal to the stenosis, pulmonary suppuration and, very frequently, pleural infection. Even if the atelectatic lung remains dry it will almost certainly fail to re-expand, and for these cases, when collapse therapy is indicated, thoracoplasty offers fewer risks and better results (Chamberlain and Gordon, 1942). The same rule applies in cases where bronchial ulceration is present, and here again thoracoplasty should be advised in preference to pneumothorax. An exception may be made, however, where the ulcers are shallow and superficial: here some good results have been reported with preliminary local treatment of the ulcerated area by the application of 30 per cent. silver nitrate. If there is satisfactory healing it may be possible to proceed with a pneumothorax without undue risk.

If, from the pool of patients considered as possible candidates for the hollow needle we eliminate those presenting the contra-indications enumerated above, the success of the procedure will then largely depend upon the management of the treatment. The unilateral case with an early lesion as a rule presents no problem: the disease process has not had time to involve the pleura to any extent, and adhesions, if present at all, are few and can be readily divided. These early cases are, however, a minority, and clinical judgment is more severely tested in the management of the moderately advanced group. It may be taken for granted that adhesions will be present in every one of these, and therefore thoracoscopic inspection of the pleural space is indicated. I will illustrate the importance of this by quoting figures from two series of cases. In his last publication on the subject, Brock (1938) reported a series of 302 cases in which he had carried out adhesion section because of ineffective collapse. In 128 of these he succeeded in freeing the lung completely; in 75, although the lung was not completely freed, a useful or satisfactory degree of collapse was obtained; while in the remaining 99 improvement was negligible. In the past five years at Tor-na-Dee 101 cases have been treated by pneumothorax, and of these 76 were submitted to thoracoscopy. Forty-eight were made effective by division of the adhesions; the remaining 28 were found to be inoperable, and we were then free to consider alternative methods of treatment. These figures will, I hope, serve to show that nowadays adhesion section (or, if one prefers the more formal title, closed intrapleural pneumolysis) is an indispensable adjunct to artificial

pneumothrax, and facilities for its performance should be available in every institution where this treatment is carried out.

From the figures it will be seen that in a proportion of cases the adhesions are indivisible—it may be on account of their thickness and extent, or because they contain lung tissue; or again there may be an actual prolongation of a lung cavity extending into an adhesion band, and here ill-judged attempts at cauterisation will succeed only in letting loose a flood of infection into the pleural space. These inoperable cases provide us with our second major point in management, namely, the imperative necessity for terminating at the earliest possible moment a pneumothorax which cannot be made effective. Delay in making this decision is exposing the patient to a needless risk: his ineffectively collapsed lung is not contributing towards his control of the disease, and the onset of a severe effusion may wreck his ultimate chances. It is better to allow him to cut his losses as soon as possible and seek the aid of surgery in time.

We may sum up the present position of artificial pneumothorax briefly, by saying that it still occupies a deservedly high place in the treatment of pulmonary tuberculosis; but it can be a two-edged sword, and should not be used too freely. It is not invariably beneficial, or even neutral, in action, but may do harm either actively by way of its complications or passively by delaying surgical collapse. The decision to use it in a particular case deserves as much thought as we give to our contemplated thoracoplasties.

Tuberculous Empyema.—Before finally quitting this aspect of collapse therapy there is something to be said about the treatment of that formidable complication, tuberculous empyema. Although, by careful selection and management of cases, its incidence can be considerably reduced, a proportion of patients in any large series will develop tuberculous pus in their pleural cavities. Until recently there was little agreement on the treatment of this condition. Aspiration was practised by some; others used various disinfectant solutions, with singularly little success; while a third group refrained from intervention of any sort. Results were thoroughly unsatisfactory, and the situation was somewhat chaotic until it was realised that the infected pleural space was analogous to an intrapulmonary cavity. It required the same sort of treatment—it had to be obliterated—and the most satisfactory method of securing its obliteration was by thoracoplasty. There is evidence in abundance supporting this present-day view. Woodruff (1938) found a mortality rate of 50 per cent. by conservative treatment alone; Brock (1943), surveying a series of 90 cases, found that of 42 treated along conservative lines 33 were dead; while of 48 who had had thoracoplasty only 7 had succumbed. Ehler (1942), in an exhaustive survey of world literature, drew the following conclusions:—(1) that tuberculous empyema was largely preventible or avoidable, (2) that it was still rather badly treated, and (3) that thoracoplasty, with or without external drainage of the

empyema cavity, had produced the greatest number of cures, with the lowest mortality.

Consider for a moment the practical problem of a case of tuberculous empyema as it confronts the physician. He must survey it from two aspects: (*a*) the empyema itself and (*b*) the intrapulmonary disease for which the pneumothorax was induced. If the collapse has been unsuccessful in controlling the pulmonary disease the problem is simple. The pneumothorax has failed in its object, it has produced a highly undesirable complication and it must be terminated and replaced by thoracoplasty at the earliest possible moment. If, on the other hand, the collapse has been effective, it may be justifiable to temporise for a short period and endeavour to clear up the pleural infection by a course of irrigation. Occasionally—very occasionally—this is successful. If response to this treatment is not apparent within a few weeks, then the only really safe course to adopt is to terminate the pneumothorax and re-expand the lung, this process of re-expansion being assisted by the continuance of the pleural lavage. Comparatively recently a new substance has been introduced for use in pleural irrigation, Azo-T solution. The initial work with this product was carried out in 1941 by Petroff, Herman and Palitz, who were dissatisfied with the results achieved by the employment of Eusol, methylene blue, Azochloramid and the various other materials then advocated. Azo-T is a mixture of Azochloramid, with the addition of a wetting agent in the form of sodium tetradecyl sulphate. This latter substance, which reduces surface tension, affects the permeability of cell membranes and bacterial envelopes and enhances the bactericidal effect of the antiseptic. The solution also has a solvent action on the necrotic material present in such cases on the visceral pleura; hence its value where pulmonary re-expansion is desired. The originators of the method claimed encouraging results in their series, and recently a further short series has been published in Britian by Ashman and Tate (1943), in which re-expansion was satisfactorily obtained in 65·2 per cent. We have been using Azo-T in selected cases at Tor-na-Dee for the past two years, and are satisfied that in it we have the most effective medium for pleural irrigation which has yet been introduced. Its main use, however, lies not so much in its antiseptic properties as in its solvent action, and with few exceptions we have used it with the object of promoting re-expansion of the lung. The treatment of tuberculous empyema has now, I believe, been placed upon a rational basis. The object is to secure obliteration of the infected pleural space. This is done, in cases where the collapse is ineffective, by thoracoplasty. Where the collapse is effective, obliteration is secured by promoting gradual re-expansion by means of a course of pleural irrigation. Should the intrapulmonary focus become re-activated during this phase, thoracoplasty again provides the solution, and though this may seem a drastic recommendation, it is infinitely preferable to the hazards of a collection of pus in the chest,

with its potentialities of bronchopleural fistula and secondary infection. In isolated instances a tuberculous empyema may pursue a benign course, as shown by the late F. G. Chandler (1942) in a very carefully selected series of 12 cases, which he had observed over a long period of years. There is, however, no method of determining which case is likely to do so, and the occasional success of non-intervention should not be taken as encouraging an all-round policy of *laissez-faire*.

Extrapleural pneumothorax, which arrived about 1936, and from which so much was hoped, has been and gone. In this operation the parietal pleura was stripped from the inner surface of the thoracic dome and mediastinum, the space thus created being maintained by refills of air. Hailed with enthusiasm by both physician and surgeon on its introduction, as offering a solution to one of the big problems of collapse therapy—the adherent apical cavity—it received a wide trial. I had the privilege of seeing a considerable number of cases done in 1937, 1938 and 1939—and the even greater advantage of seeing the ultimate results. We hoped that this would be a reversible procedure, like artificial pneumothorax, which could be applied to a localised area and maintained by refills, and that after the elapse of a sufficient period of time a healed and re-expanded apex would result—a most beautiful conception in theory, a veritable phthisiologist's dream—but in practice we found that (*a*) the extrapleural space created by the surgeon in the majority of cases became the seat of an effusion, which in absorbing caused premature re-expansion; (*b*) the effusions which failed to absorb showed a high incidence of tuberculous empyema, an appreciable percentage in addition becoming secondarily infected; and (*c*) the few cases which survived these complications proved difficult to re-expand without re-activation of the former focus. Brock, reviewing his series of cases at a meeting of the Tuberculosis Association in 1943, said that he had done 100 cases up to the end of 1939 but only 8 since. We are justified, therefore, in saying that the most recent development in extrapleural pneumothorax has been its virtual abandonment.

Transpleural Suction.—The past few years have also seen the introduction and eclipse of yet another method of intervention in pulmonary tuberculosis. In February 1939 I spent an afternoon at a Swiss clinic, where I had foregathered with some of my senior colleagues to hear a talk on a new method of treating lung cavities. The speaker was a refugee who had been working at Monaldi's clinic in Rome, but, having incurred the displeasure of the Fascist party, had had to take a hurried departure. Before leaving, however, he had had the foresight to possess himself of a series of very impressive X-rays, and it was these which he demonstrated to us that afternoon. The method to which we were introduced that day was that which about a year later was being discussed so hopefully here—transpleural suction drainage of cavities. The conception was Monaldi's, who believed that the cavity wall consisted partly of atelectatic lung tissue and that

by the insertion of a catheter into the cavity and by applying constant gentle suction, the cavity wall was first cleansed and then slowly the atelectatic tissue re-expanded, under the influence of the suction, to fill the lumen. Finally approximation of the walls took place, followed by fibrosis and healing. In theory this conception had much to commend it. The insertion of the catheter was a simple proceeding, and there were no really serious complications to be feared. Like extrapleural pneumothorax, however, Monaldi drainage proved disappointing when put to the test of time, and as a single procedure for the closure of lung cavities has now practically faded out of the picture. Holmes Sellors (1942) and Maxwell and Kohnstamm (1943) have reviewed their results, and, while recording an appreciable diminution in the size of the cavity in a goodly proportion of their cases, found that permanent closure was a rarity. Maxwell states that in his series all the cavities were reduced in size but practically all re-expanded when drainage was interrupted. Closed suction drainage, however, still retains its usefulness in a limited sphere. A patient with a giant cavity in one lung, who, as he stands, is a bad surgical risk for a thoracoplasty, may be converted into a reasonable risk by a preliminary drainage. Not only is the cavity reduced in size and thereby made more amenable to surgical collapse, but the patient's general condition improves following the institution of drainage and the relief which is afforded by the diminution of cough and sputum. In such a case the chances of a successful and permanent result from a thoracoplasty may be greatly improved by transpleural drainage for some weeks previously. Maxwell, in a personal communication, also tells me that he believes suction drainage prior to thoracoplasty is a factor in the prevention of bronchogenic spread of the disease in the post-operative phase. Otherwise I do not feel that suction drainage has now any place in the treatment of pulmonary tuberculosis.

Diaphragmatic Paralysis.—The boom enjoyed by diaphragmatic paralysis some seven or eight years ago has passed its peak, and one does not read so much nowadays about this extremely valuable little operation. Provided that too much is not expected of it, paralysis of the diaphragm still retains a very useful place in the treatment of pulmonary tuberculosis. Its chief indications are to control lesions situated in the mid and lower zones of the lung, to supplement a pneumothorax and to correct the mediastinal displacement caused by a fibrotic lung. It is a relatively simple operation which carries little risk and causes no disfigurement—factors which, perhaps, have caused it to be more widely used at times than circumstances warranted. Phrenic paralysis may be permanent or temporary—the nerve may be evulsed or it may be crushed. When it is crushed, diaphragmatic function is abolished for an average period of six months, and the chief development to record is the greatly increased tendency to use the temporary rather than the permanent operation. During the past five years we have carried out 88 phrenic operations at Tor-na-Dee,

50 temporary and 38 permanent. In the past year the proportion has been 24 temporary to 1 permanent. Our predilection for the crush as opposed to the evulsion is first of all a natural reluctance to use an irreversible procedure when a reversible will suffice. Furthermore, following an evulsion, the permanent decrease of respiratory function might be a disadvantage should a partial thoracoplasty be required at a later date. There is also evidence strongly suggesting that a paralysed diaphragm on the affected side increases the risk of spread to the lower lobe during thoracoplasty. Where there are definite indications for a permanent diaphragmatic paralysis, as in a fibrotic lung with mediastinal displacement, then the evulsion is obviously the operation of choice; but otherwise a crush is to be preferred. If pulmonary relaxation is desired for a longer period than the usual six months conferred by the crush there is no objection to recrushing the nerve a second, or even a third, time.

Artificial Pneumoperitoneum.—In conjunction with diaphragmatic paralysis another procedure calls for consideration—the institution of an artificial pneumoperitoneum, which has been receiving considerable attention in this country during the past two years. Banyai (1934) and Joannides and Schlack (1936) did a great deal of the pioneer work on the subject, and were impressed by the additional elevation of the hemi-diaphragm which followed the induction of a pneumoperitoneum in cases treated by phrenic paralysis. Case results are now appearing in the literature, and, while it is yet too early to arrive at a fully reasoned estimate of the value of the procedure, there is sufficient evidence to show that it definitely has a place in the treatment of pulmonary tuberculosis. Used in association with phrenic paralysis its indications are those for the temporary operation, and it would appear to exercise its most beneficial effect on lesions at the lung base and below the clavicle. My own personal experience so far is limited to 16 cases, all done within the past two years. Of these 16, 9 were successful, while the remainder were completely unaffected. It is, of course, quite out of the question to attempt to draw any conclusion from such a small series, except that the number of successes fully justifies the use of the method, particularly as it is readily reversible, subjects the patient to little inconvenience and has few complications.

If extrapleural pneumothorax and Monaldi drainage have raised our hopes only to dash them again, we can still take courage from the development and continued success of *thoracoplasty*. The most formidable procedure of all, it nevertheless gives the most consistently satisfactory results of any form of collapse therapy, provided it is applied with understanding and care. As originally practised, the operation consisted of removal of the posterior segments of ribs, thus reducing the size of the hemithorax and securing lateral relaxation of the diseased lung. It produced no vertical relaxation, and cavity closure was achieved only in about 35 per cent. of cases. In 1936, however, the whole position was revolutionised by the work of Semb

of Oslo, who introduced the modern operation, in which, in addition, to rib resection, the apex of the lung is mobilised in the plane of the endothoracic fascia, thus securing vertical relaxation. This is now the accepted operation, and in a recent paper Price Thomas (1942) has pointed out that its use has doubled the number of favourable results achieved by lateral thoracoplasty alone.

I do not propose to go into details regarding the indications for thoracoplasty. The ideal case is the strictly unilateral one with a strong tendency to fibrosis, who is non-toxic and apyrexial. To restrict the operation entirely to patients presenting these criteria would be to narrow its field very considerably, and experience has shown that these indications may be extended, with a reasonable hope of achieving a satisfactory result. Disease in the contra-lateral lung does not now rule out thoracoplasty, providing it is limited in extent and is either quiescent or at least has been shown to be non-progressive for a period of months. Intermittent bouts of pyrexia indicating periodic activity need not contra-indicate, providing the operation is timed to coincide with a period of comparative quiescence; and there is even a field for operation where the disease is slowly progressive and the patient very gradually going downhill. This type, however, carries a definite mortality, and the greatest care is necessary in the selection of cases and in the management of the pre- and post-operative phases.

Thoracoplasty may be partial or complete. For a considerable time the complete operation held pride of place, but now a more conservative procedure has come into favour and the minimum number of ribs necessary to secure effective relaxation is resected.

In the past five years 17 patients have had thoracoplasty operations at Tor-na-Dee. A survey of results shows that, of these 17, 12 are completely recovered, are T.B. negative and have resumed their former occupation; one other is well and working, but still has occasionally a trace of positive sputum; 2 are improved but not working; and 2 died shortly after operation.

Thoracoplasty is no longer a last resort in the treatment of tuberculosis, and where the indications for the operation are presented it should not be delayed in an over-optimistic attempt to save the patient from mutilation. It is not, however, a proceeding to be indulged in unless both the physician and surgeon in charge of the case have had considerable experience in thoracic surgery. A high degree of specialised surgical skill is required, and there is no room for haphazard selection of cases or for inadequate pre-operative and post-operative care. Close co-operation between physician, surgeon, anæsthetist and specially trained nursing staff is essential if consistently good results are to be obtained, but, given good judgment and enthusiasm, the results will justify the work involved. Unlike many other forms of collapse therapy, thoracoplasty is irreversible: a failed case means a thoracic cripple.

Resection.—Before finally leaving the realms of surgery, I might

just refer briefly to some of the very latest work, which is not as yet beyond the trial stage. The success of resection of a lung, or of a lobe, in the treatment of bronchiectasis and certain early cases of pulmonary neoplasm made it inevitable that radical removal of a tuberculous lung would yet be considered. The nature of the disease and its reluctance to remain localised to one particular area for any length of time suggest that the field for radical surgery will ever be a restricted one, but up to the present a limited number of successes has been recorded (Alexander, Sommer and Ehler, 1942; Behrend, 1943). The only indications which have been put forward with any assurance are complete bronchial stenosis, the presence of a tuberculoma in the lung and old arrested pulmonary tubercle with much fibrosis and bronchiectatic change. These conditions have been successfully dealt with, but at present it is difficult to see how the indications can be extended.

Surgery in the treatment of pulmonary tuberculosis is no longer an innovation. It passed the experimental stage years ago, and its record during the last ten years is impressive. It is, of course, applicable only to a limited number of cases, but for these cases it can do what nothing else can do—it can rescue them from chronic invalidism and convert them into useful economic units again. Furthermore, there are many cases of advanced tuberculosis in the wards of our hospitals and sanatoria who would at one time have been suitable for surgery and who could have been rescued from their present predicament had the facilities been more widely available. The memorandum recently issued by the Society of Thoracic Surgeons of Great Britain emphasises these points and outlines a scheme for the organisation of thoracic surgery on a regional basis throughout the country. At present skilled chest surgery is available only at comparatively few centres, yet the need is such that any scheme for the treatment of tuberculosis demands that it should be readily available wherever required. The surgeons' Memorandum deserves the wholehearted support of every physician who treats this disease.

In discussing collapse therapy and the surgery of pulmonary tuberculosis I have said little about cases of bilateral disease. These are always problems, and each one must be judged on its merits, but even here there is a field for the judicious use of collapse methods. A bilateral pneumothorax is common; a shallow pneumothorax on one side may be combined with an upper thoracoplasty on the other; or we may utilise a phrenic crush and a pneumoperitoneum to control the less affected lung, preparatory to a thoracoplasty on the remaining side.

Chemotherapy has so far contributed little to the therapeutics of pulmonary tuberculosis. Gold salts for many years were used freely, but are now passing out of favour. There was never any marked concensus of opinion upon the indications for their administration, there was little uniformity in the results obtained and their toxicity was by no means a negligible factor. They have been employed less

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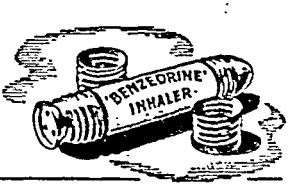

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and less of recent years, and we are likely soon to see them vanish completely from our dispensaries.

The advent of the sulphonamides gave rise to some hope that one or other of the various compounds would be found to be effective against the tubercle bacillus, and much work has been and still is being done in this connection. It was soon seen that none of the usual compounds exercised any appreciable effect, and research was directed further afield. The sulphone group came under review, and in 1940 workers at the Mayo Clinic found that tuberculosis in guinea-pigs could be controlled by one of these compounds, to which the name " promin " was given. Clinical trials followed, and in Britain a series of cases of pulmonary tuberculosis were treated by Heaf, Hurford, Eiser and Franklin (1943). Results, however, were indefinite, and these workers concluded from their trials that promin was not the desired medicament for the cure of tuberculosis, although it was probably a pointer in the search for it. Since then two other compounds have been introduced—diasone, which is similar in chemical constitution to promin and apparently resembles it in its action and effects, and promizole, which, from the very cautious reports at present to hand (Feldman, Hinshaw and Mann, 1944) appears to be the most promising chemotherapeutic product which has so far been studied in tuberculosis. This product is effective in guinea-pigs in a dosage half that of promin, and clinical trials are now proceeding, the Mayo Clinic workers having administered it to a series of 56 cases. Their preliminary report early in 1944 (Feldman, Hinshaw and Pfuetze) made no attempt to assess results—it will obviously be many months before such an evaluation can be attempted—but they do seem to have established that promizole can be administered in large dosage with only the mildest and most transient of toxic effects.

In Sweden, too, chemotherapeutic research is proceeding, and Willstaedt (1944) is continuing his attempt, first published in 1942, to find a compound combining fat solubility and bacteriostatic action on the tubercle bacillus. That a drug will eventually be found which will be more lethal to the tubercle bacillus than its host appears now to be within the bounds of probability; but we are not yet within sight of our goal, and the greatest care will be necessary lest premature or ill-founded conclusions are drawn from any of the experimental work now proceeding. Disillusionment affects morale, and the maintenance of morale is a vital point in the management of the tuberculous patient.

One word of warning regarding the possible place of chemotherapy in pulmonary tuberculosis. This is a destructive disease, and, though the drug may have a bacteriostatic effect on the bacillus, the disorganisation of the lung tissue will still leave us with the problems of fibrosis and secondary bronchiectasis. No magic white pill is likely to rid the patient of the cough and dyspnœa consequent on extensive scarring, and the advent of the looked-for panacea should be a signal for an even more intensive drive for early diagnosis.

Pleurisy and Primary Pleural Effusion

The developments dealt with so far have been concerned with the case of established disease, the case with a definite intrapulmonary focus, and have taken no account of pleurisy and primary pleural effusion. It is now well recognised that the tubercle bacillus is the causative factor in the great majority of these cases, but there is still some difference of opinion as to whether sanatorium treatment should be advised, and, if advised, for how long it should be carried out. In many instances no definite evidence of an active pulmonary focus can be found, and there is a disinclination on the part of the patient to label himself tuberculous by entering a sanatorium, with all the implications of such a course. Heaf and Hillingworth (1944) have given a short preliminary report on the establishment in 1942 of a unit of 130 beds, at the Queen Mary Convalescent Hospital at Sidcup, for the observation, assessment and treatment of cases of pleurisy, pleural effusions and minimal lesions of pulmonary tuberculosis. Intensive investigation of each case is carried out, and every effort made to establish a correct diagnosis. Treatment is by means of an initial period of bed-rest, never less than six weeks, followed by graduated convalescence and rehabilitation. This enterprise represents a real advance in the management of potentially serious conditions, and further reports from this new unit will be awaited with great interest.

B.C.G. Vaccine

Finally a word must be said about the work which has been done in Norway on the production of a relative immunity to tuberculosis by means of B.C.G. This vaccine, prepared from a special non-virulent type of bovine bacillus, has been used from 1927 to 1939 as a protective measure in nurses and medical students who were tuberculin negative on entering hospital. Vaccination with B.C.G. was offered to all with a negative tuberculin test, but was not compulsory, and those who declined vaccination formed a control group. The follow-up figures of the groups showed that among nurses the total morbidity of tuberculous illness per year of observation was 17·1 per cent. in the non-vaccinated group and 2·6 per cent. in the vaccinated group, while among students the figures were 4·3 per cent. and 1·2 per cent. respectively (Hansen).' These figures are very striking, and as a result of their experiences the Norwegian workers had planned a series of mass investigations, which were intended in due course to include the whole country. The investigation was to be by means of mass radiography and tuberculin testing with B.C.G. vaccination of those found to be tuberculin negative. Unfortunately the German invasion intervened and the plans did not materialise. B.C.G. has not been used in Britain so far, but these figures from Norway are so impressive that there would seem to be a good case for investigation

here into the potentialities of this vaccine as a means of protection in young adults.

In this review of the present position of the therapeutics of pulmonary tuberculosis there has been no epoch-making discovery to record, no dramatic high-light comparable, for example, with the introduction of thiouracil. The story is one of a slow but steady advance along orthodox lines, an advance in which we are learning to use the methods at our disposal more effectively and perfecting our technique in the field of collapse therapy. It is not a discouraging picture: we can offer the tuberculous patient much more to-day than we could ten years ago, and the excursions into the byways of chemotherapeutic research which have already taken place hold out a good hope that our explorations in this direction will yet result in the discovery of a hidden pass through the mountain barrier of the disease.

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FURTHER EXPERIMENTS IN THE STUDY OF IMMERSION FOOT

By W. BLACKWOOD and H. RUSSELL

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Introduction

IN a previous paper [1] a histological study was made of the changes which occur in the tail of the rat after periods of exposure to cold and wet. The periods and conditions of exposure were comparable with those under which the less severe forms of immersion foot develop in man. It was found that conspicuous damage to the muscle and nerve tissues was present after exposures of 48 hours and increased with longer exposures and that the skin and other tissues, including blood vessels, appeared to be much more resistant to chilling. The nerve and muscle tissue had not returned to normal in animals killed sixty days after exposure: and in rats surviving two months there was some evidence that muscle degeneration secondary to denervation was setting in. Treatment in the form of two heating-up processes was investigated. They were found to accelerate the initial reaction, but made no significant difference to the histological changes in a month's time.

In view of these findings and because of the histological abnormalities found in the extremities of human cases which have long survived exposure, [2, 4] it was considered advisable to continue the study in rats surviving exposure for a longer time, *i.e.* between 90 and 365 days, to see if there was any further restitution towards or departure from normality.

Experiments

The experiments were performed upon rats, and the tail was used as an experimental limb. The animals were exposed in a cold room (Temp. 3° to 4° C.). The cages were so arranged that cold artificial sea water trickled slowly through them but never reached a depth of more than about half an inch. The water in the cages was usually about 1° warmer than the air of the cold room. Food and water were suspended within reach from the cage roofs, and under these conditions the lower part of the hind legs and the tail of the rat were almost continuously immersed. It had been found that exposure to this wet and cold for more than 96 hours approached the fatal time for laboratory rats, and that 48 hours was the minimum of exposure required to produce definite damage to nerve and muscle. Accordingly rats exposed for 48 and 96 hours were used. Table I is a summary of the experiments and shows that they were subdivided into two series, depending upon the temperature at which the rats were allowed to recover from the exposure.

Series A.—The animals were allowed to recover slowly without any question of treatment, spending the first twenty-four hours after "rescue" in an unheated room (average temp. 13·5° C.) and then being transferred to the animal house (average temp. 18° C.).

TABLE I

	Series A.		Series C.	
	Slowly Warmed up after Exposure.		Warmed up in Air Incubator at 37° C. for Three Hours after Exposure.	
	Rat No.	Survival Time.	Rat No.	Survival Time.
48 hours' exposure	224	92 days	223	88 days
	225	92 „	...	...
	232	180 „	229	165 days—found dead
	233	180 „	234	180 days
	239	365 „	235	180 „
	240	365 „	...	...
	...	...	...	...
96 hours' exposure	226	90 days	227	90 days
	228	90 „	...	...
	231	145 „	230	150 days—found dead
	238	180 „	237	180 days
	236	183 „	...	...
	...	...	241	365 days
	243	365 days	242	365 „

Series C.—The animals after rescue were heated up in a 37° C. hot air incubator for three hours before being put in the animal house.

(In the previous set of experiments a series B was present, in which the animals were warmed up rapidly in shallow water at 29° C. for half an hour after "rescue." As there was no histological difference between the B and C series it was not further studied.)

Preparations Examined

In all rats a transverse section of the centre of the tail was embedded in celloidin and sections were stained with hæmatoxylin and eosin, and by Masson's tri-chrome method.

Longitudinal fillets of the soft tissues near the central point of the tail were studied in frozen sections, stained by Anderson's method for myelin and by Weddell's modification of Bielshowky's stain for axis cylinders. The fillets were taken with their mid-point 60 mm. from the tail base except in the case of rats 228, 238, 242 (55 mm.): 226, 243 (50 mm.): 241 (45 mm.): 239 (40 mm.): 240 (20 mm.).

Details of Series A

Rats were exposed to cold and wet for 48 and 96 hours and were allowed to survive for varying periods thereafter, from 90 to 365 days. After exposure they were allowed to *warm up slowly* in an unheated room before being put into the animal house.

Rats exposed for 48 hours.—In all rats the bone, blood vessels and cutaneous tissues were healthy. In those surviving for 92 days the picture was com-

paratively normal. There were a few muscle fibres which were unusually slender and which were hypernucleated. Some of the muscle-nerve leashes contained slightly fewer myelinated nerve fibres than normal. Motor nerve endings were visible on the muscle fibres. In rat 224 the presence of "ultra-terminal" nerve fibres and nerve fibres wandering between the muscle fibres were evidence of regeneration of motor nerves.[3] There was no significant fibrous tissue increase. The main nerves were well myelinated. In the 180-day survivors the histological picture was similar. In the 365-day survivors the picture in rat 240 was normal; in rat 239 (with a longer tail) there were focal areas of abnormality in two main muscle bundles, with diminution in muscle fibre calibre, with much endomysial fibrous tissue thickening: other tissues appeared healthy.

Rats exposed for 96 hours.—In all rats the bone, blood vessels and cutaneous tissues were healthy. In the 90-day survivors the muscle fibres were sometimes small and hypernucleated, and in rat 228 there was fibrous thickening of the endomysium (Fig. 1). The main nerves had lost about half

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FIG. 1.—Rat 228, exposed for 96 hours (A series), survival time 90 days. Transverse section of tail muscle and main nerve. To show slenderness of many muscle fibres and slight fibrous thickening of the endomysium. ×85. Hæmatoxylin and Eosin.

FIG. 2.—Rat 236, exposed for 96 hours (A series), survival time 183 days. To show practically normal muscle fibres. ×85. Hæmatoxylin and Eosin.

FIG. 3.—Rat 243, exposed for 96 hours (A series), survival time 365 days. To show an almost normal picture. There is still some variation in muscle fibre calibre and muscle nuclei sometimes lie within the fibre. ×85. Hæmatoxylin and Eosin.

FIG. 4.—Rat 237, exposed for 96 hours (C series), survival time 180 days. To show marked fibrous thickening of the endomysium. ×85. Hæmatoxylin and Eosin.

FIG. 5.—Rat 228, exposed for 96 hours (A series), survival time 90 days. To show demyelination of main nerve. ×350. Anderson's myelin stain.

FIG. 6.—Rat 243, exposed for 96 hours (A series), survival time 365 days. To show re-myelination of main nerve. ×350. Anderson's myelin stain.

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their myelinated fibres but many unmyelinated regenerating fibres were present (Fig. 5). In the muscle nerve leashes there was often only one normal myelinated fibre present but there would be several regenerating unmyelinated or finely myelinated fibres (Figs. 7, 9). Re-innervation of muscle fibres was present, numerous motor nerve endings being visible (226). In a 145-day survivor, rat 231, the muscle damage was severe, with numerous small hyper-nucleated muscle fibres and endomysial fibrous thickening. Main nerves were better myelinated, but no motor nerve endings were seen. The 180-day survivor showed a much less extent of muscle damage. The 183-day survivor (Fig. 2) and the 365-day survivor (Fig. 3) were similar and nearer to normal. They showed no areas of fibrosis in the muscle. There was some variation in muscle fibre calibre, so that some were a little more slender than normal but they were well innervated by leashes full of myelinated fibres (Fig. 8). The main nerves had not quite returned to normal (Fig. 6).

DETAILS OF SERIES C

The rats were exposed for 48 hours and 96 hours and allowed to survive for 88-365 days. After exposure they were *warmed up* for three hours in a 37° C. hot air incubator.

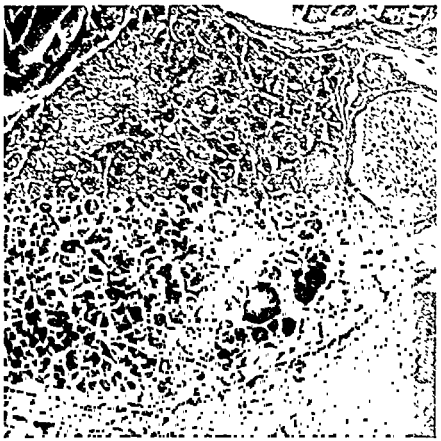


FIG. 1.

FIG. 2.

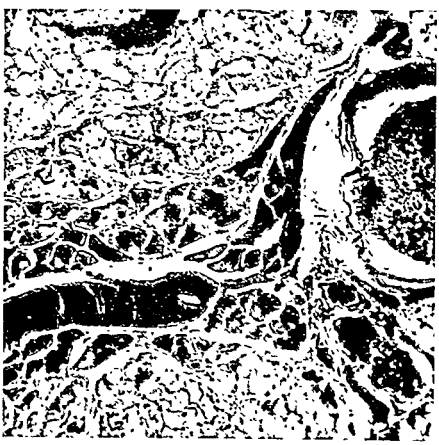
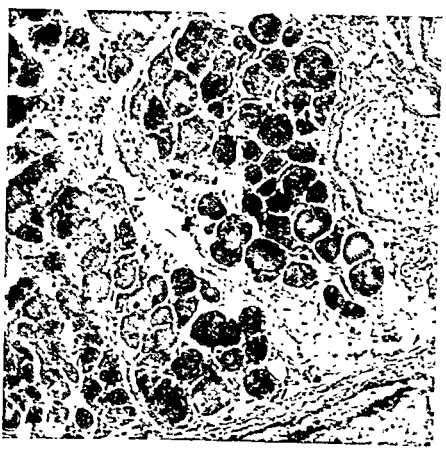


FIG. 3.



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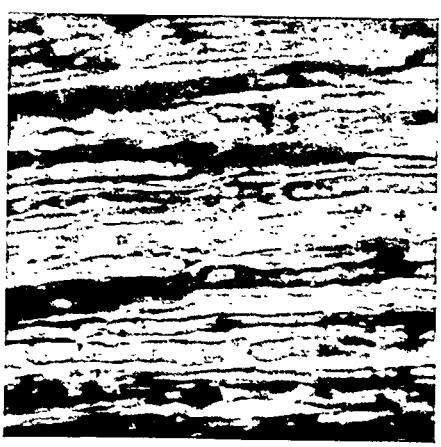

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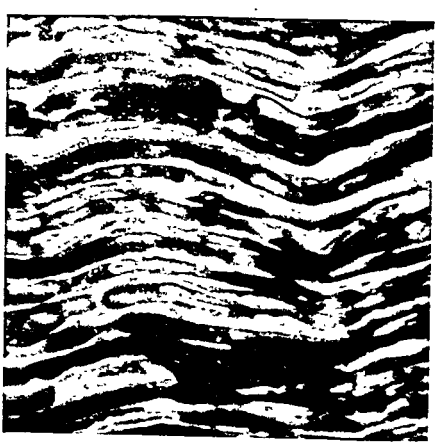

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

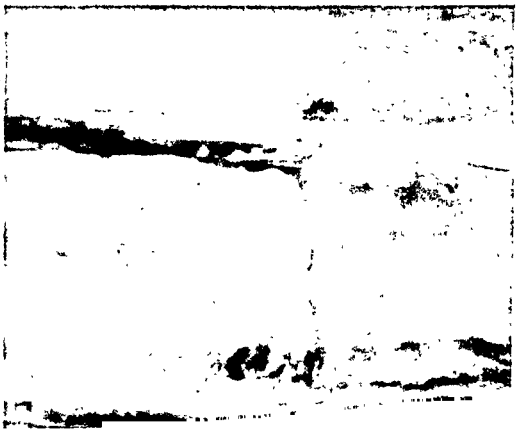

FIG. 10.

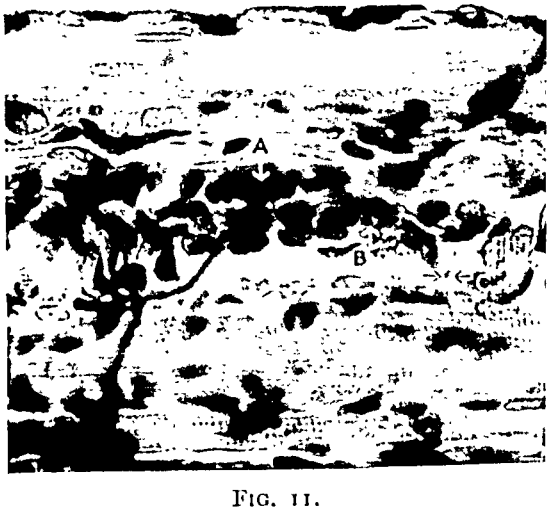

FIG. 11.

Rats exposed for 48 *hours.*—In all rats the bone, blood vessels and cutaneous tissues were healthy. The picture in the 88- and 180-day survivors was similar to that in the A series. Rat 229, 165-day survivor, which was found dead in its cage one morning, showed nerve regeneration similar to the others but numerous muscle fibres were still small and hypernucleated and there was a fibrous thickening of the adjacent endomysium.

Rats exposed for 96 *hours.*—In all rats the bone, blood vessels and cutaneous tissues were healthy. A 90-day survivor was similar to that in the A series. The 150-day survivor, which was found dead, the 180-day survivor (Fig. 4) and one 365-day survivor, rat 242, all showed numerous small hypernucleated muscle fibres with endomysial fibrous thickening and few or no motor end plates visible. Rat 241, the other 365-day survivor, did not show any fibrous tissue increase and the variation in muscle size was less noticeable. The main and muscle nerves showed a progressive remyelination which in 365 days had almost reached normal.

FIG. 7.—Rat 228, exposed for 96 hours (A series), survival time 90 days. To show one large and one fine myelinated nerve fibre in a muscle nerve leash. ×350. Anderson's myelin stain.

FIG. 8.—Rat 243, exposed for 96 hours (A series), survival time 365 days. To show re-innervation and myelination of a muscle nerve leash similar to the previous figure. ×350. Anderson's myelin stain.

FIG. 9.—Rat 226, exposed for 96 hours (A series), survival time 90 days. To show a muscle nerve leash with one large, probably myelinated nerve fibre and fine regenerated fibres. ×350. Weddell's modification of Bielschowsky's stain for axis cylinders.

FIG. 10.—Rat 236, exposed for 96 hours (A series), survival time 183 days. To show a nerve fibre which has left its neurilemma tube and is " wandering " across two muscle fibres. ×300. Weddell's modification of Bielschowsky's stain for axis cylinders.

FIG. 11.—Rat 237, exposed for 96 hours (C series), survival time 180 days. To show one of the few re-innervating muscle nerve fibres. This fibre is re-innervating two motor end plates A, B, and then proceeds as an " ultraterminal " fibre C. ×350. Weddell's modification of Bielschowsky's stain for axis cylinders.

Discussion

The aim of these experiments was to continue the investigation of the histological changes which take place in the tail of the rat, after exposure to conditions comparable with those under which immersion foot develops in man. In previous experiments [1] the tissues had been examined at intervals from 1 to 60 days after exposure. In this further series the process was studied from 90 to 365 days after exposure.

It was found that, under the conditions of the experiment, the main changes, as in the previous series, were in nerve and muscle, the other tissues being relatively unaffected. In nerve and muscle, despite individual variations, there was progress towards the restoration of the histological normal. As might be expected, rats which had been exposed for 48 hours showed a more rapid histological recovery than rats which had been exposed for 96 hours. In both 48- and 96-hour exposures the *nerves* showed a steadier progress than the muscles. In the 48-hour rats of both A and C groups the nerves reached a state close to normality by 92 days : in the 96-hour rats progress was steady

and similar in the A and C groups, but even after 365 days the average size and density of myelinated fibre in the main nerve was not quite equal to the normal.

In the *muscle* more individual variation in the extent and degree of persisting abnormality was apparent and it showed itself in the narrow calibre of the fibres and in hypernucleation and endomysial fibrosis. In the 48-hour rats muscle damage was very little except in rats 239 (A/365 day) and 229 (C/165 day). In the 96-hour exposure rats the C series showed more persistent muscle damage and more endomysial fibrosis than the A series. When one considers the extent and severity of the muscle damage seen shortly after exposure in the 96-hour rats [1] it is remarkable what degree of restoration towards normal was shown in 365-day survivors, *e.g.* rat 243, A series (Fig. 3), and rat 241, C series: on the other hand, rat 242 (C series/365 day) still showed considerable damage and some fibrosis.

The 96-hour rats in which persistently small hypernucleated fibres and endomysial fibrosis were found were those in which few or no motor end plates were visible; whilst motor end plates (even though imperfectly formed and regenerating) were always visible in comparable sections from tails with healthier looking muscles. It is reasonable therefore to suggest that failure to re-innervate and persistent small muscle fibre size run hand in hand, and re-innervation of regenerated muscle fibres is compatible with restoration of normal structure. It was not possible to decide whether the endomysial fibrosis was the cause or the sequel of the failure of innervation. Even in the relatively healthy looking muscle some degree of obstruction of the neurilemma tubes of the regenerating nerves must have been present, for the presence of "escape," "wandering" or "ultraterminal" fibres (Fig. 10) suggests that it was often as easy for the returning stream of axoplasm to burst out of the neurilemma tube as to force its way into the old end plate. Similar appearances are to be seen in animal muscles in which the only pathological process has been nerve crushing or nerve section and suture.[3]

Summary

1. A histological study was made of the changes which occur in the tail of the rat, 90 to 365 days after exposure to cold and wet. The periods and conditions of exposure were comparable with those under which the less severe forms of immersion foot develop in man.

2. As before, the brunt of the injury fell on the neuro-muscular apparatus.

3. The nerves now showed a slow progressive return towards normal.

4. There was a marked individual variation in the amount of persisting muscle damage, which appeared to be correlated with an absence of re-innervation of motor nerve endings.

5. Treatment, in the form of heating up to 37° C. in hot air, appeared to have a slightly adverse effect upon muscle recovery.

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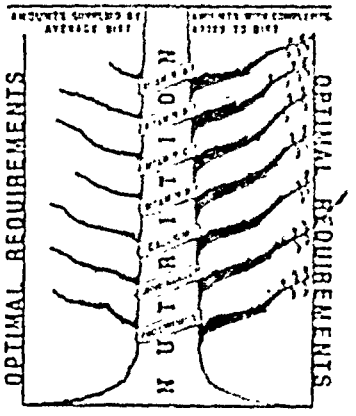

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Conclusion

From this group of experiments and the previous study [1] it can be seen that the tissues in the rat's tail most directly affected by exposure to cold and wet are the nerves and striped muscles. These tissues degenerate to an extent which depends upon the duration of exposure. The damaged nerves regenerate, axis cylinders first growing down and then becoming myelinated. The damaged muscle fibres also regenerate but fail to regain full histological normality unless they manage to make contact with motor nerves. The extent to which this successful contact is made is in some cases very great and the remarkable degree to which some of these muscles and nerves recover is due, no doubt, to the initial escape from damage of the neurilemma and the sarcolemma, so that there is no serious mechanical obstruction to regeneration.

It is perhaps well to remember that the tail of the rat is very well supplied with arterio-venous anastomoses and may therefore be more able to recover rapidly from spells of cooling than the limbs of man.

We have once more to thank Professor Drennan for his interest in and criticism of this study, and Professor Daly for the use of the cold chamber in the Physiology Department.

We are indebted to Mr J. Sommerville and Mr R. Allen for their fine histological preparations, and to Mr T. Dodds for the microphotographs, and we have to thank the Moray Fund for a grant to cover the cost of the experiments.

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LOW BLOOD PRESSURE

By J. G. M. HAMILTON, M.B., F.R.C.P.Ed.

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IN any consideration of the subject of low blood pressure it is necessary to decide upon a reasonable meaning for the term and to attempt a broad classification which will separate such disorders as are incidentally accompanied by low blood pressure from those in which the low blood pressure is, or may be, the major factor.

Accepted figures for the normal standards of human blood pressure have undergone considerable change since the introduction of the mercurial sphygmomanometer and the auscultatory method of measurement, and the tendency has been consistent for progressively lower standards to be established. The traditional formula of 100 plus the age in years has long been abandoned, since this formula yielded figures for maximum normal systolic blood pressure in adults which were too high. Furthermore, this formula gave no indication of a range of normal figures and paid no attention to the diastolic pressure. I am not mainly concerned at this time with the maximum normal blood pressure, but rather with the figures which can be accepted at the lower range of normal. It is the case, however, that there has been a progressive reduction in the accepted maximum, as more and more attention has been paid to the early stages of hypertension, often symptom-free.

For many years 110 mm. of mercury was accepted as the minimum normal systolic blood pressure in adults (Halls Dally, 1929; Treadgold, 1933; Rook and Dawson, 1938), and figures below this level were regarded as indicating hypotension, though MacWilliam (1925) held that "roughly anything decidedly below 100 mm. systolic, or 60 mm. diastolic, may be suspected of being abnormal." Systolic blood pressures of 105 mm. or less disqualified from flying in the U.S. Army Air Corps in the period prior to 1936 (Snell, 1936). Subsequent regulations, however, permitted a minimum of 100 mm. for flying duties (Rook and Dawson, 1938). In all cases, of course, satisfactory results of general and special examinations were also required. However, the admission to flying duties of men with systolic pressures as low as 100 mm. indicates a lowering of the acceptable standards of normal systolic blood pressure. Alvarez and Stanley (1930), after examining 6000 fit prisoners in American jails, considered that 90 mm. was the lower limit of normal systolic pressure,

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 7th September 1944.

and White (1944) admits systolic pressures of 95 mm. to be normal. Robinson and Brucer (1939), after a very critical analysis of insurance figures, obtained from large numbers of persons in all age groups, arrived at the conclusion that the normal range of the systolic blood pressure was 90 to 120 mm. for all adult ages. If these observations and analyses are accepted—and there seem to be good grounds for admitting their validity—many people must be considered normal in so far as their blood pressure is concerned, who formerly would have been classed as hypotensive.

One important reason for this reduction in the standards of normality has been the recognition of the falsity of arguing from arithmetical averages of blood pressure, even of large groups of persons, since those averages include the blood pressures of individuals who are actually suffering from hypertension in its earlier stages. There is increasing recognition also of the fact that normal blood pressures, both systolic and diastolic, rise but little with age, and hardly at all before the age of forty-five (Alvarez and Stanley, 1930; Robinson and Brucer, 1939). MacWilliam (1925) also held the view that "the idea of an extended progressive rise in systolic blood pressure in healthy persons, as life goes on, is erroneous." Instead of considering average blood pressure in apparently normal people, it is more accurate to lay weight upon the most common or modal blood pressure, as an expression of normality. Of all the 3677 fit white prisoners, aged fifteen to eighty-four years, examined by Alvarez and Stanley, the modal systolic blood pressure was found to be 114·4 mm.; while the modal diastolic pressure between the ages of fifteen to twenty-nine years was 68 mm., and between the ages of thirty to eighty-four years, 73 mm. Robinson and Brucer, after excluding from their series all persons with pressures above 140/90 mm., admittedly abnormal, found the modal systolic blood pressure of 6485 men, aged fifteen to eighty years, to be 115·1 mm., and the modal diastolic pressure, 73 mm. The largest age group examined, thirty to thirty-four years, with 1125 men, showed a modal systolic figure of 113·3 mm. and a modal diastolic figure of 73·1 mm. Three thousand and fifteen women, aged fifteen to seventy-nine, gave modal systolic and diastolic pressures of 111·6 and 70·3 mm. respectively, while in the largest age group examined, thirty to thirty-four years, with 586 women, the respective figures were 112·5 and 67·1 mm. These authors believe from analysis of their figures that normal blood pressures do not rise with age, though hypertensive and so-called pre-hypertensive blood pressures do. This evidence indicates that the most common normal adult blood pressure is in the region of 115/70 mm. with a systolic range of 90/120 mm.

Apart from considering simple observations and critical analyses of the blood pressures of large groups of supposedly healthy people, it is justifiable in assessing the normality or otherwise of low blood pressures to take account of mortality rates. Blood pressures which

are undoubtedly accompanied by high mortality rates cannot be considered normal, even though persons possessing them are apparently healthy at the time of examination. The very large experiences of North American life insurance companies provide clear evidence not only that the mortality of persons with blood pressures above 140 mm. systolic and 90 mm. diastolic is much higher than the mortality of those with lower pressures, but also that the mortality declines notably the lower the pressure, being lower for instance in groups with pressures of 110 70 mm. or less, than in groups with pressures of around 120/80 mm. (Robinson and Brucer). The mortality rate of 3389 persons, aged sixteen to sixty years, with systolic blood pressures of 100 mm. or less, reported by Friedlander (1924), was only 35 per cent. of the expected rate. MacWilliam (1925) held that low blood pressure, after the age of fifty with no organic lesion to account for it, constitutes the best criterion of life beyond the normal expectancy.

The observation has frequently been made that in the earlier stages of essential hypertension, the blood pressure, systolic and diastolic, is liable to considerable fluctuations, now rising into the range of frank abnormality, now falling to levels of doubtful normality. As the years go by, the general level is set progressively higher though the fluctuations persist. Robinson and Brucer followed 500 apparently fit men in all adult age groups over a period of ten years by annual observations of the blood pressures made under very strict and admirable conditions. Those men—and they fell into all adult age groups—who showed systolic pressures of less than 120 mm. at the beginning of the period, showed no tendency to increasing pressure and showed only small fluctuations. Further, the fluctuations were smaller in those starting with systolic pressures below 110 mm. than in those starting with pressures between 110-120 mm. In the groups commencing with systolic pressures over 120 mm. there was a clear tendency for the pressures to rise with age to hypertensive levels and the annual fluctuations were much wider; or, as these authors put it, "the excursions into the danger-zones of hypertension were more frequent." It is on the basis of these analyses that they conclude that 120 mm. should be regarded as the upper limit of normal. Although this figure is considerably lower than the usually admitted maximum and may not be generally acceptable until further confirmation is forthcoming, it may be said confidently that healthy adults of all ages with systolic blood pressures below 120 mm., and particularly those with pressures below 110 mm., have the assurance that they are most unlikely to become hypertensive. This is manifestly of great significance, since hypertension and its effects constitute one of the most important of the killing diseases, particularly in an ageing population.

Apart from the problem of longevity, the question may be asked: Is persistent low blood pressure compatible with good health? In examining this question it is immediately apparent that if persistent

low blood pressure were itself a disease or were a common predisposing condition to disease, the mortality rates for those exhibiting it would not be better than the rates for those with so-called normal pressures of 120-130 mm. systolic and 80-85 diastolic.

Halls Dally (1929) enunciated what he called "The Biological Law of Hypopiesis," namely that low blood pressure—and he took 110 mm. as the minimum normal systolic pressure in adults—is always to be regarded as an expression of a low vitality state. He held that the subjects tended to be of poor bodily build, thin and pallid with narrow chests and small elongated hearts, and that they were "deficient in calcium and other vital salts." This seems to me to be typical of the kind of loose thinking which has clouded the subject in the past, and it has left an aftermath of opinion which is not adequately supported by more critical observation and analysis. Cambridge athletes were studied over a period of many years by Michell (1909) who found that they frequently showed resting systolic blood pressures of 95/110 mm. Of 60 doctors and medical students, aged eighteen to forty-seven years, examined by Chamberlain (1930), 15 showed systolic blood pressures below 110 mm. Of those, one suffered from cold hands and chilblains, and one suffered from cold hands and what was called "neurasthenia." All the remainder were of good physique and health and were athletic in greater or less degree. Of 28 Marathon runners at the Amsterdam Olympic Games in 1928—the cream of the long-distance runners of all nations—7 had systolic blood pressures (measured before the race and with the subjects under optimum conditions) of 110 mm. or less, and the third place in the race was taken by a man aged thirty-one years, with a resting pressure of 105/70 mm. (Bramwell and Ellis, 1931).

Treadgold (1933), after analysing observations on the blood pressures of 20,000 R.A.F. pilots over a period of twelve years, concluded that there was one group of hypotensives (systolic pressure below 110 mm.) who exhibited a high degree of cardiovascular efficiency; and that hypotension, even below 100 mm., can, and frequently does, co-exist with a high degree of general physical efficiency.

Rook and Dawson (1938), also basing their conclusion on the examination of R.A.F. pilots and candidates for flying duties, state that persistent hypotension (systolic pressures below 110 mm.) is not necessarily accompanied by symptoms. It is compatible with good health, and if so, piloting duties are permissible. Hypotension and poor vasomotor control, as judged by flying tests, do not necessarily occur together.

Almost 50 per cent. of the women under forty years, 34 per cent. of those over forty, and 25 per cent. of all men of the large insurance series examined by Robinson and Brucer (1939) had systolic blood pressures below 110 mm. Kreienberg and Winter (1941) report that persons with "hypotonia" always have high altitude tolerance. On

the other hand, Young (1941), analysing 159 fatal air crashes held on enquiry to be due to mistakes on the part of the pilots, found that 73 per cent. of the pilots had shown some form of hypotension. However, he does not describe the forms of hypotension involved, nor does he indicate the frequency of blood pressures of different levels among the general body of pilots.

It is quite evident from those and many other observations that systolic blood pressures persistently in the range between 90-110 mm. are perfectly compatible with long life, vigorous health and a sufficiently high degree of general and cardiovascular efficiency to satisfy the strict criteria of health imposed by the Air Forces of Great Britain and the United States, and to permit successful endurance of the enormous strains associated with modern military flying. There has been much discussion about the factors which contribute to poor flying tolerance, and as yet there is no single test for any man's ability to be a good pilot. While, so far as I am aware, the U.S. Army utilises, in some measure at least, the complicated Schneider index, based on changes in pulse rate and blood pressure between the lying, sitting and standing positions, the R.A.F. have come more and more to depend on a thorough general physical examination, together with a general assessment of the candidate's ability, balance and aptitude in both the physical and psychological senses. There seems now to be sufficient evidence that the poor vasomotor control which goes with dizziness, faintness and "black-outs" in flying is found in pilots with so-called normal blood pressures, as well as in those with so-called hypotensive pressures. It may be the case that it is less the level of the blood pressure than the general state of vasomotor control and the psychological balance of the pilot which are the critical factors in ability to withstand flying stresses. It is justifiable to take it that systolic pressures in the range between 90-110 mm. should be accepted as normal except when there is other evidence of disease.

Hypotension is often regarded as being a premonitory sign of pulmonary tuberculosis. It is true that many patients with active tuberculous disease exhibit hypotension. That low blood pressure alone is not a reliable sign in the early case has been stressed by MacWilliam (1925) and Fishberg (1932); but it is generally agreed that hypotension combined with signs and symptoms of pulmonary tuberculosis indicates activity, and persistent and inreasing hypotension is probably a bad prognostic sign.

Low blood pressure, by which is usually meant a systolic pressure below 110 mm., is often held to be an important factor in the causation of a large group of symptoms, notably low-grade physical and mental stamina, dizziness, fainting attacks, palpitation, sensitiveness to cold, liability to dyspepsia, etc. It is frequently reported that low blood pressure is most often to be found in persons of asthenic habitus (Rolleston, 1928; Halls Dally, 1929; Fishberg, 1932; and Goldberg, 1942). Most authors are agreed that persons with low blood pressure

are liable to be thinner than average. Alvarez and Stanley (1930) found that thinness tended to be associated with pressures in the lower ranges after the age of thirty-five years, but they found no correlation between blood pressures and what they called stockiness and ranginess. That the clinical features just enumerated are due to low blood pressures in the order of 90-110 mm. can no longer be held.

Records of 53 consecutive patients of my own have been examined, whose predominant complaints were prolonged fatigue, lassitude, fainting turns, " black-outs," dyspnœa, dyspepsia, etc., in explanation of which no organic lesion could be demonstrated and of which emotional disturbance was held to be the cause. These patients ranged in age from eighteen to sixty-four years. Six had systolic blood pressures of 110 mm. or less, with ages between twenty to forty-four years ; 13 had diastolic pressures of 70 mm. or less, with ages between eighteen to fifty-three years ; 11 had diastolic pressures of 90-105 mm. with ages between forty-three to sixty years, together with one patient aged twenty-six years. It is probable that in this series more attention should be paid to the diastolic than to the systolic pressures, since fluctuations due to temporary causes such as excitement usually induce smaller changes in the diastolic pressure than in the systolic. Although every precaution was taken to obtain reasonably accurate blood pressures by having the patients at rest, warm and composed, it is likely that some systolic readings were higher than they should have been. However, there is no indication from this admittedly small series that hypotension is any more common than hypertension in patients complaining of the symptoms commonly attributed to hypotension. It was in fact much less common than blood pressures in the so-called normal range. These patients were thoroughly studied, and in all a diagnosis of psychoneurosis was reached. Douglas-Wilson (1944), describing the somatic manifestations of psychoneurosis in 231 soldiers, emphasises dizziness, palpitation, " black-outs," sighing for breath as common features, in addition to dyspnœa and precordial pain, found in the cardiovascular form of neurosis. White (1944) states that in neuro-circulatory asthenia in which persistent dizziness, faintness, palpitation, dyspnœa, fatigue, precordial pain, sweating and nervousness are characteristic features, the blood pressure shows no typical abnormalities, tending on the whole to be slightly elevated and variable. The symptoms commonly attributed to hypotension are in fact found equally, if not more often, in persons exhibiting normal or raised blood pressures. They are manifestations of emotional disturbances, operating in all probability through functional derangement of the autonomic nervous system. It is quite understandable that moderate and persistent hypotension should sometimes occur in such circumstances as part of the expression of the basic disorder. Ferris, Capps and Weiss (1937) found that, although the carotid sinus was often hypersensitive in patients suffering from vegetative neuroses, surgical denervation of the carotid sinus did not alter the

symptoms. *If a systolic blood pressure of 90-110 mm. is found in* persons presenting symptoms of fatigue, lassitude, dizziness, etc., it is often the only concrete physical finding, and as such may be credited with the causation of the symptoms. Many doctors are still loath to make a diagnosis of psychoneurosis and prefer to fasten upon such an apparent physical defect as providing a more tangible explanation of the clinical picture. This is the more unfortunate as the patient, too, offered the diagnosis of low blood pressure, accepts this as an understandable physical explanation. Although I do not think that in the lay mind the diagnosis of "low blood pressure" carries the serious and dangerous connotation which is carried by "high blood pressure," yet, *such is the layman's interest in and ignorance of the* physiological concept of blood pressure, this diagnosis may be utilised *by the patient as an admirable excuse for unnecessarily restricting his* physical effort and for continuing to suffer from his symptoms. Like "tired heart," "strained heart" and "false angina," the diagnosis of "low blood pressure" is, if given to the patient, a potent influence in the perpetuation of his psychoneurosis, for in addition to providing him with a convenient physical explanation, it may prevent the proper handling and treatment of the fundamental emotional disorder.

It must further be emphasised that hypotension is not an expression of cardiac disease, with certain exceptions which should be readily recognisable, *e.g.* coronary thrombosis, paroxysmal tachycardia, cardiac tamponade and aortic stenosis. None the less, it is not uncommon to find patients with systolic blood pressures in the lower ranges who have been told they have low blood pressure due to cardiac weakness, and who often on this account unnecessarily abstain from ordinary physical exercise.

Attempts to raise the blood pressure by means of pressor agents such as adrenalin, ephedrine, benzedrine and pituitrin, or with proprietary glandular extracts of doubtful composition and more doubtful potency, are usually unavailing and misguided in so far as relieving the symptoms is concerned. When symptomatic benefit occurs, it is usually temporary, and there is no proof that it is not due either to the cortical stimulant action of ephedrine or benzedrine, or to pure suggestion. In view of the normal day-to-day fluctuations in blood pressure, an increase of 5-10 mm. in the systolic pressure, sometimes hailed with joy as indicating successful therapy, cannot be regarded as of any significance.

It is notable in psychoneurotic patients with blood pressures of 90-110 mm. that, at such times as the anxiety or other underlying emotional disturbance is less evident, not only are the general symptoms relieved but the blood pressure reading may be somewhat higher. Conversely, when the emotional disturbance again becomes prominent, the blood pressure may gradually fall to the lower levels. This is by no means invariable, however, and many such patients show blood pressures in this range when they feel well and when they feel ill.

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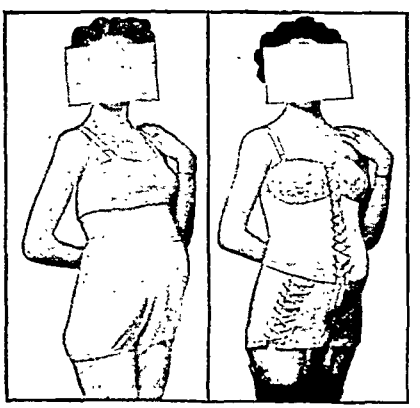

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So-called hypotension acquired and stubbornly retained its significance as at least a disorder if not a disease, because a fall in the blood pressure is associated with the weakness, depression and maybe collapse and death of such acute conditions as syncope; primary, hæmorrhagic, traumatic and anaphylactic shock; severe bacterial and protozoal infections; coronary and mesenteric thrombosis; pulmonary embolism; paroxysmal tachycardia; dissecting aortic aneurysm; and acute abdominal catastrophes such as acute pancreatitis; or such chronic conditions as chronic infective and cachectic diseases, including turberculosis and Addison's disease.

In discussing the part played by the hypotension itself in the production of symptoms in these disorders, it seems necessary to consider them in three groups :—

(1) In the case of acute and chronic infective diseases, traumatic, burn and dehydration shock, and Addison's disease, there is great disturbance of general bodily function, produced by bacterial toxæmia, by gross derangement of colloid and fluid balance and by disorder of salt and water metabolism respectively. There seems to me to be no satisfactory evidence that the general weakness, sense of fatigue and fainting are produced by the hypotension, rather than by the primary disorder. The fall in blood pressure is itself a manifestation of the primary disorder.

(2) In the case of syncope, whether of vasovagal type or due to hypersensitivity of the carotid sinus, primary and hæmorrhagic shock, and paroxysmal tachycardia, there is little doubt that the faintness and loss of consciousness are directly due to cerebral anæmia, consequent upon the sudden fall in blood pressure.

(3) In the case of coronary thrombosis, pulmonary embolism, dissecting aortic aneurysm, and acute abdominal catastrophes, more than one factor is probably involved. The features of shock, including a fall in the blood pressure, may appear immediately or may be delayed for some hours or for a day or two. These conditions are associated as a rule with discomfort which is often extreme and may, particularly in the case of coronary and pulmonary occlusion, be accompanied by great mental distress and apprehension. It is probable that the sudden development of features of shock, including the fall in the blood pressure, is due to neurogenic factors, similar to those causing the primary shock of more benign types of bodily injury. In coronary and pulmonary occlusion the sudden cardiac embarrassment is doubtless a contributory factor, but the fact that a similar clinical picture is found in mesenteric thrombosis and dissecting aortic aneurysm suggests that cardiac embarrassment is not the main cause. In pulmonary occlusion it is obvious that the main sudden strain is applied to the right ventricle and yet there is marked drop in the blood pressure in the systemic arterial tree. The occlusion of a major pulmonary vessel may, of course, bring this about merely by restricting the pulmonary blood flow and consequently the supply to the left

ventricle, but when the occlusion involves a smaller pulmonary branch, this factor cannot be great. Even a small coronary occlusion is followed by a drop in the blood pressure, but it is not easy to imagine that the injury to the myocardium, which may be minute relative to the bulk of uninjured myocardium, should cause an immediate and marked reduction in expulsive power. The delayed shock and lowered blood pressure in these conditions may be due to the general action of the products of autolysis in the damaged tissue. Moon (1944) and many others have recorded evidence that traumatic shock, with or without bacterial infection, may be due to autolytic toxæmia. It must be pointed out, however, that this view of the pathogenesis of traumatic shock has not yet received general acceptance. It is likely, however, that the delayed shock following crush injuries is due to the liberation of some toxic substance from the injured structures (Bywaters and Beall, 1941).

Whether hypotension *per se* causes clinical features or not is dependent upon the rapidity and degree of the fall in blood pressure, and upon the length of time over which it is maintained at frankly low levels. A sudden fall in blood pressure, as in simple syncope, or after a large hæmorrhage, or in postural hypotension is associated with faintness or loss of consciousness, and it matters little whether the preceding systolic blood pressure was 250 or 100 mm. On the other hand, a gradual fall in systolic blood pressure to 80 or 70 mm. occurs in Addison's disease, without fainting or other unequivocal symptom of circulatory failure. When frank hypotension, for example a systolic pressure of 80 mm. or less, is rapidly developed and maintained, the clinical picture of the causative disorder is complicated by the effects of diminished renal filtration pressure, namely, oliguria or anuria with nitrogen retention and uræmia.

I wish now to discuss the condition known as postural or orthostatic hypotension. This is characterised by the occurrence of faintness or loss of consciousness on rising from the recumbent to the erect posture. Bradbury and Eggleston (1925) first fully described this disorder and gave details of their study of 3 patients in whom the blood pressures fell sharply from normal or elevated levels in the recumbent position to pressures of the order of 40-50 mm. systolic and 25-40 mm. diastolic in the erect position with loss of consciousness. Further cases were recorded by other observers, including Ghrist and Brown (1928), Croll and Duthie (1935), Ellis and Haynes (1936), Korns and Randall (1937, 1938), MacLean and Allen (1940), and Stead and Ebert (1941). The clinical pictures of the original cases of Bradbury and Eggleston included not only syncope on standing up but also deficient or absent sweating, loss of libido and potency, secretion of more urine in the recumbent than in the erect posture, a failure of the pulse rate to rise on standing up and a sensation of persistent fatigue. Stead and Ebert observed a loss of reflex vaso-constriction in response to a fall in arterial pressure. These additional

features have not been observed in all the recorded cases. In many there has been evidence of organic disease of the central nervous system, such as tabes dorsalis, syringomyelia and subacute combined degeneration of the cord, but in others no such signs were obtained. Stead and Ebert believe that the condition is due to lesions of the sympathetic centres or their efferent tracts in the spinal cord. Postural hypotension often occurs in the post-operative period after splanchnicectomy for hypertension. Although in some cases the recumbent blood pressures are low, in others the recumbent pressures are normal or even elevated. In some cases the symptoms are most pronounced in the morning when the patient rises from his bed and tend to diminish in severity as the day goes on (MacLean and Allen). The name orthostatic hypotension has been given to such cases.

In normal subjects the mechanism of vasomotor control is so nicely balanced that very little change occurs in the blood pressure on voluntary or passive change from recumbency to the erect posture. Schneider and Truesdell (1922) studied 2000 normal men. On active voluntary change from supine to erect posture the systolic pressure showed a mean rise of 2·3 mm. and the diastolic pressure a mean rise of 8 mm. Mortensen (1923) studied 90 normal women. On passive change from supine to erect posture on a tilting table the systolic pressure showed a mean fall of 4 mm. and the diastolic a mean rise of 8 mm.

The sharp postural fall in pressure occurring in patients with postural hypotension is illustrated by the following cases :—

1. Supine blood pressure 128/98 mm. ; erect 58/40 mm. (Ghrist and Brown (1928).
2. Supine blood pressure 170/120 mm. ; erect 80/70 mm. (Croll and Duthie, 1935).
3. Supine blood pressure 125/80 mm. ; erect 55/40 mm. (Korns and Randall, 1938).
4. Supine blood pressure 130/85 mm. ; erect 90/70 mm. in a case of my own (Fig. 1).

Intermediate values are usually obtained in the sitting posture. A similar, though less marked, postural reduction in blood pressure is frequently found in association with the hypotension of Addison's disease, but without symptoms. This is illustrated by the case of Ghrist and Brown in whom the supine blood pressure of 78/58 mm. fell, when the patient stood up, to 60/54 mm., and by a case of my own in whom the supine pressure was 112/75 mm. and the erect pressure 85/65 mm. (Fig. 2).

It is usually considered that postural hypotension is due to a failure of splanchnic vasoconstriction to offset the gravitational effects of the assumption of the erect posture, and, in so far as a drop in pressure is obtained in changing from lying to sitting, this is likely to be the case. Although some patients complain of dizziness or even faint when

they sit up, in others the symptoms do not occur until the body is erect. The improvement which may follow the application of a firm abdominal

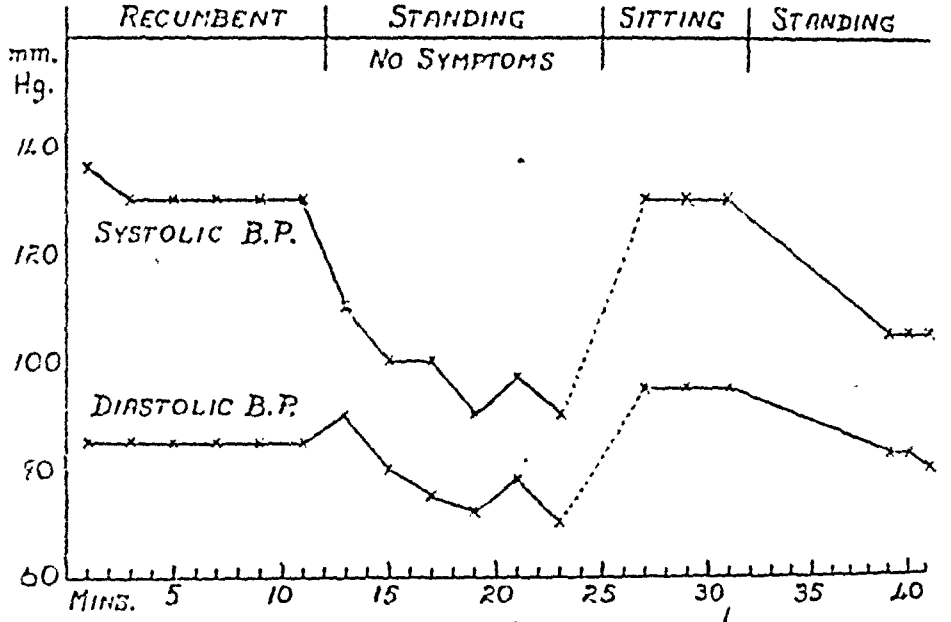

FIG. 1.—Female æt. 15.

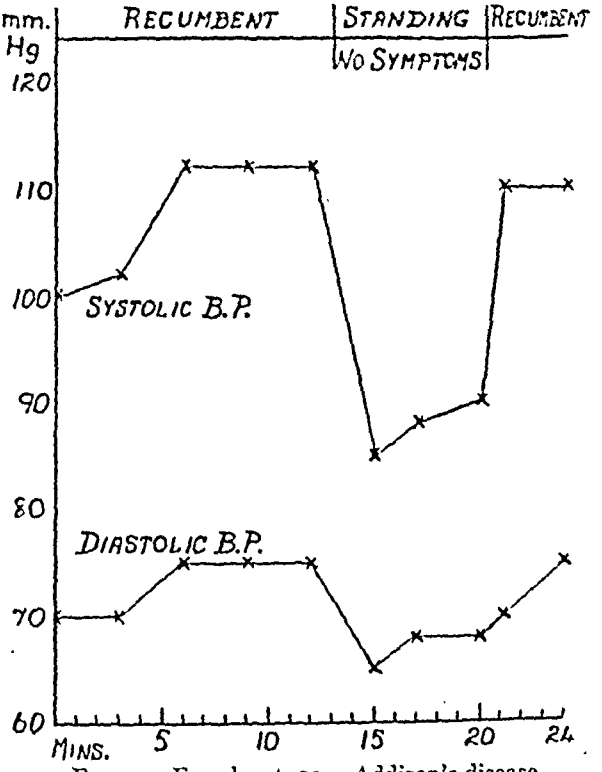

FIG. 2.—Female æt. 33. Addison's disease.

binder is doubtless due to the increased pressure upon splanchnic vessels and consequent assistance to the venous return to the heart. MacLean and Allen believe that the defect is not a lack of tone in the

splanchnic arterioles, but rather a dilatation of venules, supporting their view by the observation that patients with orthostatic hypotension have a " lack of potential " in the venous return to the heart, as shown by the Flack test. This test consists of blowing against a mercury manometer with the glottis open, thereby increasing intrathoracic pressure against venous return. Normal persons can hold the column at 40 mm. for at least twenty-five seconds with little change in pulse rate or blood pressure, whereas patients with orthostatic hypotension become pulseless and collapse within ten seconds.

That the postural drop in blood pressure in these patients and after splanchnicectomy for hypertension is not due to laxity of the abdominal wall is suggested by the observation that section of all the intercostal nerves on both sides, paralysing the abdominal muscles, was not followed, in a patient with advanced organic hypertension, by a drop in blood pressure on standing (Roth, 1935).

However, the abdominal binder is not always effective. MacWilliam (1933) produced good evidence that in normal subjects the rise in heart rate, the slight rise in diastolic pressure and the maintenance of systolic pressure were partly dependent upon afferent impulses derived from the thighs, and he believed that these were of greater importance than impulses arising in the splanchnic area. Croll and Duthie (1935) studied a patient suffering from postural hypotension in whom little beneficial effect was obtained by the application of an abdominal binder. The application of tourniquets round the thighs markedly diminished the extent of the postural drop in blood pressure. It is perhaps significant in this regard that their patient exhibited the Holmes-Adie syndrome of absent knee-jerks and tonic pupil, and that other cases of postural hypotension have suffered from tabes dorsalis and subacute combined degeneration of the cord. The possibility that the postural defect is due to some interference with reflex pathways has been suggested.

Adrenaline, ephedrine, benzedrine and paredrine have been used in treatment with variable success. Ghrist and Brown (1928) obtained relief in one patient by giving 25 mg. of ephedrine (approximately $\frac{3}{8}$ gr.) hourly for 9 doses a day and later 50 mg. thrice daily. Korns and Randall (1937) obtained benefit with 192 mg. of ephedrine (approximately 30 gr.) a day in divided doses. Their patient preferred benzedrine which they next used, great improvement being achieved with 100-150 mg. a day. The same authors subsequently (1938) treated the disorder with a combination of benzedrine and paredrine. Used separately these drugs had very similar pressor effects, but the patient preferred benzedrine since it diminished his lassitude, suggesting that the fatigue so characteristic of orthostatic hypotension was not due entirely to the low blood pressure. These authors gave 20 mg. of benzedrine at 6 a.m. and 7 a.m. and 40 mg. of paredrine two-hourly, from 8.30 a.m. to 2.30 p.m.

The beneficial effect of ephedrine, benzedrine and paredrine,

however, seems to decline with use. The pressor action raises the whole level of the blood pressure but does not permanently prevent the postural drop according to MacLean and Allen (1940).

Strikingly beneficial and lasting results were obtained by MacLean and Allen and confirmed by Corcoran *et al.* (1942), in cases of orthostatic hypotension by the use of a tilted head-up bed. After sleeping for a few nights with the head end of the bed raised some 18 in. the patients experienced no symptoms on rising in the morning and no significant postural drop occurred in their blood pressures. When they were restored to sleeping on a level bed the vertigo and syncope on rising in the morning quickly returned, as did the postural hypotension. The features were once again abolished by sleeping on the tilted bed and remained in abeyance indefinitely as long as the patient continued to sleep in this position. It appears that a postural vasomotor mechanism depending upon the influence of gravitational pressure on abdominal vessels or vessels in the lower limbs was depressed by sleeping in the recumbent position. There is an obvious and interesting connection between these observations and those of MacWilliam (1933) on the influence of afferent impulses from the vascular circuit of the lower limbs in the postural control of blood pressure.

I wish to stress the fact that all patients complaining of vertigo or fainting on rising from the recumbent to the upright posture do not suffer from postural or orthostatic hypotension. A woman aged thirty-six complained of dizziness on getting up in the morning. Postural blood pressure observations showed a perfectly normal response, the recumbent pressure being 110/70 mm., and the erect pressure 105/80 mm. (Fig. 3). Another woman aged forty-six, complaining of dizziness, precordial pain and dyspnœa on sitting up, also had a normal postural pressure regulation with a recumbent pressure of 100/63 mm., and an erect pressure of 110/70 mm. (Fig. 4).

However, the changes in blood pressure on change of posture of patients who exhibit these symptoms should be studied, since if postural or orthostatic hypotension is demonstrated, material benefit can usually be obtained by the use of an abdominal binder, by the administration of ephedrine, benzedrine or paredrine, or, possibly best of all, by the use of the tilted head-up bed.

Summary

1. The literature on the limits of normal adult blood pressure is briefly reviewed.

2. Ninety mm. should be regarded as the lower limit of normal rather than the more commonly accepted figure of 110 mm.

3. Systolic blood pressure in the range 90-110 mm. is frequently found in normal persons at all ages, and is compatible with long life, good health and a high degree of physical efficiency.

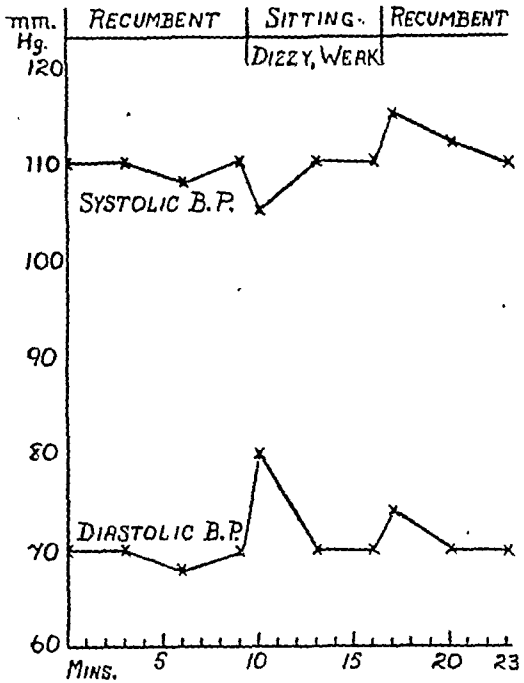

FIG. 3.—Female æt. 36.

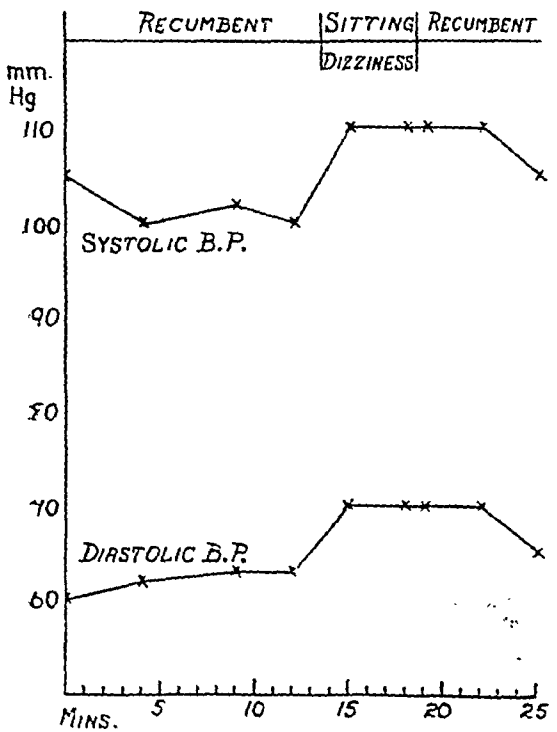

FIG. 4.—Female æt. 46.

4. Adults possessing blood pressures in this range are unlikely to develop essential hypertension.

5. Poor vasomotor control and systolic blood pressure of 90-110 mm. do not necessarily occur together.

6. The symptoms of persistent fatigue, dizziness, fainting attacks, etc., are not due to persistent hypotension, being frequently found in association with "normal" or elevated blood pressure. These symptoms are frequently due to psychoneurosis.

7. Symptomatic hypotension is discussed.

8. Postural and orthostatic hypotension are discussed.

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DIAGNOSIS AND DESCRIPTION OF CANCER *

By W. F. HARVEY, M.A., M.B., F.R.C.P.Ed., Lieut.-Colonel I.M.S. (ret.), Superintendent and Histologist, Laboratory, Royal College of Physicians, Edinburgh.

I. INTRODUCTION

MY subject requires a little comment. The words "diagnosis of cancer," or "cognition of cancer," may be paraphrased as "Seeing through Cancer" (διάγνωσις, knowledge especially of a higher kind; deeper vision). My subject, therefore, is capable of a wide range of treatment, and I shall make no attempt to explain any apparent digression in which I may indulge. I have no illustration of an objective kind with me, no lantern slides, no microscopic slides. I confess, therefore, to being a transgressor of the truth expressed in the saying :—

> "Segnius irritant animos demissa per aurem
> Quam quae sunt oculis subjecta fidelibus."

The word cancer is used in the sense of malignant tumour, whether carcinoma or sarcoma or other malignant neoplasm, and I do not insist on any absolute distinction between benign and malignant new growths.

Much that has been said before, much that has been read before, may with advantage be said again, either in confirmation or in criticism, especially if it is no armchair product, but the outcome of concentration on everyday experience and experiment. My own daily routine at a central laboratory has been largely restricted to reporting on the microscopic appearances of fresh surgical material and, to a very considerable extent, reporting on cancer. That does not mean that my department could truly be described as the "Dead Material Department"; it was once so described by a former colleague of my own. Actually he used a more opprobrious epithet than "material." The real pleasure obtained from microscope reporting is not in the simple attainment of a positive diagnosis; it is in the opportunity afforded of reading into the picture the state during life, the evolution and course of the condition which a section displays or explains, the relation of that picture to the journey from the egg to the grave, a true "biopsy" survey. It is unfortunate that one should have at this early stage to refer to the grave as entering into the language of description or reporting of new growths, but when one is signing daily reports, of which several are death-warrants, there is no concealing the seriousness of the responsibility involved. Biopsy reporting

* A lecture delivered 23rd November 1944 at the Royal Victoria Infirmary, Newcastle-upon-Tyne, as one of the autumn course of scientific meetings, by invitation of the North of England Branch of the British Medical Association and the Newcastle and Northern Counties Medical Society.

is not *post-mortem* reporting, and this gives it its really bright side, for the possibility of early recognition of cancer by "biopsy" after the clinical examination holds out a good prospect of cure. Cure I have always felt is better medicine or perhaps, I should say, affords greater personal satisfaction than prevention. Cure is *better* than prevention, or shall I say: prevention and cure, like benign and malignant tumours, are one and indivisible. Much, too, that is called prevention is really cure of antecedent disorder.

I have passed through my laboratory and recorded between 1st January 1929 and 31st December 1944, 19,296 tumours. I have already analysed these tumours so far according to site, sex and age, and could, I thought, have brought that as a subject before you, but it might have been too dry. My choice, therefore, has been a more general one. These 19,296 tumours have been indexed, cross indexed, reported on, discussed personally and are ready for use and research by any worker in easily available collection form. I may be permitted to claim that this is a representative collection. It must, it does, contain illustrations of cancer in almost every form. My collection, I feel, is as yet little explored. I have with my colleagues made some attempt to use it in a work entitled *Debatable Tumours*. That title was described by one pathologist friend as requiring courage, since, all tumours are debatable, and by another as "appalling." I may leave this introduction with an apology, which is for the egotistical approach to my subject; it is valedictory.

II. Diagnosis

1. *Diagnostic Method.*—Let us follow our material for diagnosis from the surgeon to the laboratory and up to the reporting stage. The out-patient room or operating theatre should have in readiness fixative, such as 10 per cent. formalin, in wide-mouthed containers, and the material should be placed at once or as quickly as possible into the fluid. A reasonably large amount of fixative is required, and on no account should the tissue be crammed into its receptacle. On no account should it be left on dry gauze or allowed to dry. For many years past I have received hundreds of specimens in fluid from Kansas City, U.S.A., which have travelled perfectly and preserved their cytological characters. Latterly, owing to war difficulties of transshipment, these tissues came all together, as many as twenty in one bottle of fixative, each with a number label threaded to it. On the whole, transsection of the material for section is best left to the pathologist, because a much better surface is obtained after than before fixation. Larger specimens are more difficult to send in fluid fixative. They may, then, be sent simply moist and in bulk, but on no account must material, large or small, be sent to the laboratory in dry gauze only. The threads of the gauze act as capillary drains and the tissue is desiccated, and converted to a horny mass throughout or, at least, on the outside. Drying of any sort must be avoided. The result for

histology is disastrous. A specimen may be wrapped in gauze well soaked in 10 per cent. formalin which is then covered by rubber or other impermeable material.

The specimen, having arrived at the laboratory, is examined in conjunction with the information notes of data and requirement. It is, if large enough, transsected, the lesion if possible identified and portions taken for section which shall include both affected and unaffected tissue. If there are special appearances which the surgeon wishes to have cleared up, they will be indicated in the accompanying notes, and it may be well to mark carefully any special spot for section. This is, of course, the procedure in all histology laboratories, and is only mentioned in order to emphasise the desirability of having unaffected, as well as affected, tissue for examination and such simple data as will ensure a reasoned diagnosis instead of a bare report. The next stage is passage from formalin fixation to Zenker or Helly's fluid for further fixation, as it has been found that, provided the stay in formalin has not been too long, a Zenker post-fixation gives good uniform tissue for section, and especially good cytology. In my laboratory, where a large volume of material is handled daily, its further passage is in wire baskets with compartments in the ordinary way, except that at one stage a continuous water pump vacuumisation is used for the removal of chloroform from the paraffin. In this way, and with present staff, thirty-two sets of specimens can be put through at once. The specimens are ready for cutting, staining and reporting in five to six days. The final diagnosis is then proceeded with and a somewhat regular method of phrase reporting followed. All tumours are indexed under (1) type and (2) locality, with details of age, sex and duration of symptoms included on the cards. Many other features which make their appearance in sections, peculiar features, normal and abnormal features, teaching and research features, are entered likewise in another index system, thus constituting a collection, not only of tumours of types and localities but one serving many other general pathological and research purposes.

A very brief account has been given of the usual procedure to obtain sections for routine diagnosis, but it not infrequently happens that the date of convenient operation, the urgency of the condition, or the convenience of the patient requires some acceleration. It is usually assumed that this need is met by the frozen section and a telegraphic report. I am not a great supporter of the frozen section. Frozen sections *can* give the answer required, but I am doubtful whether this procedure is very much advance on purely macroscopic diagnosis. I should not care to take responsibility for a verdict in doubtful cases on a frozen section, but would insist on the thin paraffin section. Such a section can, if the tissue is placed at once in fixative at operation, be taken through rapidly in eighteen to twenty-four hours, with satisfaction to the histologist. The procedure to give this requires, however, individual attention, and cannot be imposed very frequently on a laboratory dealing with much material unless, of

course, there be sufficient staff to cope with such "urgent" cases. For this rapid paraffin section one prefers to have a reasonably large area for examination, and this is not contraindicated. What is essential for rapid hardening, fixation, clearing and embedding is that the specimen shall not be too thick; penetration must be rapid.

Our own particular routine staining methods are, no doubt, conditioned by the mass production in which the laboratory is engaged. I use practically only one staining method—Weigert's iron hæmatoxylin and eosin, carefully controlled microscopically for cytological differentiation, and it seems to be entirely successful. I eschew therefore special stains unless, of course, for special purposes. My contention, right or wrong, is that silver impregnation, Van Gieson stain, phosphotungstic hæmatoxylin, etc., merely throw up cell products such as collagen, elastin, reticulin and so on, which is excellent for photographic or demonstration purposes. These stains, however, will not suffice tinctorially to distinguish cells, such as fibroblasts, myoblasts and cells of the neurilemma sheath. In this I admit I stand to be corrected. My opinion is that malignant cells are recognisable in good sections by their situation, their shape, cytoplasm and nuclei, their tissue pattern and the organ in which they are found. There is valid argument, of course, for the use of special staining in hæmatology, for pigments, mucin, fat, myelin and glycogen, but this does not represent to any extent a cancer problem.

Biopsy is a term which is used extensively in the sense of diagnosis on small fragments of picked tissue. The better it is picked the more likely it is to be satisfactory for examination, and one may enter a plea for as large a portion of tissue as possible together with adjacent tissue and some tissue in depth as well as of surface. At the same time I never cease to be astonished at the certainty with which one can diagnose bronchogenic carcinoma, from Newcastle, from a piece no larger than the head of a small nail. It must imply, I think, great accuracy of technique in procural. One of the arguments which is from time to time raised against biopsy is that of the danger of dissemination of cancer. There are few pathologists, I imagine, who subscribe to the idea of danger, and there is no doubt whatever of its great advantage for diagnosis. It may be well to draw attention to the fact that the pathologist operating on biopsy material for his diagnosis is not on the same plane as the morbid anatomist with post-mortem examination and post-mortem material. His tissue or tissues are, to say the least, small, but he does his best with them. He may, however, claim the greater importance, because his patient still lives. There is no finality in the expression "confirmed histologically"; one would indeed rather say "supported histologically." Correctness of diagnosis, nevertheless, *demands* histological support. The idea of clues followed by the detective to obtain a solution seems to me to be a good one, and would comprise the clinical, radiological and pathological pathways. The series of clues, of pathological significance, should all be set out, and these will constitute under description

a differential as well as the single positive diagnosis. These clues represent variables and are taken two, three or four at a time up to a probability which may become a mathematical certainty—the positive diagnosis in the great majority of cases. This is the apex of the diagnostic cone or the focal point of the narrowing diagnostic beam.

In dealing further with this matter of diagnosis of tumours, one may refer to the personal experience which supports the diagnosis, the recognisable tumour tissue patterns, and to the fact that the experience gained, even in a central laboratory, is never complete. Caution, too, is always required where similarity of appearance is the argument for identity. I remember asking a noted pathologist whether I might quote his authority for the conclusion come to and being rebuked by the remark, "Not authority, but opinion." Diagnosis, too, requires co-operation—the co-operation of the three major individuals concerned, surgeon, radiologist and pathologist; the pathologist, usually coming last in order, is entitled to receive all the findings of his predecessors. It is to be remembered that the pathologist is a doctor and is interested in patients, symptoms and findings of any kind. He is always very pleased to receive a provisional diagnosis as a basis of discussion. The pathologist, too, has his obligation to the practitioner. In the old Regulations for the conduct of my own laboratory I find it laid down: "Only the facts will be reported. The interpretation of the facts will be left to the person receiving the report." With that rule I entirely disagree, and I may say it has been ignored.

The surgeon looks at the cancer, feels it; the radiologist looks at it likewise, and when the material comes to the pathologist he looks at it and feels it before submitting it to transsection. His first and most important operation with the microscopic section is to look at it first with a high-power, well-corrected hand lens. This, if used with concentrated attention to visible detail, may of itself give him his full diagnosis, and is extremely important in locating areas in the section for low and high-power microscope examination. The use of the hand lens I find should be automatic procedure both before and after the use of the microscope, especially when reporting on a large scale and under pressure of time. I might dilate here on pitfalls for the pathologist, such as the mistake of taking the retracted epithelium of a duct or the detached intima of a blood vessel for contained tumour in a lymphatic, and the snare of similarity of text-book illustration with the microscopic picture, but it would lead me too far afield. One of my card-indexed titles is "misleading structure," and at the present moment gives me 1068 definite references to my own routine collection of slides.

Finally, I may say again that, as large-scale centralised reporting involves daily the decision on a major operation for the human being, the diagnosis is not a light responsibility. Amputation of limb or lung, uterus or breast, may depend largely upon the laboratory finding.

The diagnosis of cancer by biological, chemical and serological

methods has not yet yielded much fruit, but the phenomenal accuracy of diagnosis of pregnancy by gonadotropic hormones contained in the urine and the abundance of sexual hormone in pregnant mare serum give promise that perhaps that type of assay may render great service in the future diagnosis of cancer. It already does so for what might be called the gonadal and sexual tumours of testicle, ovary and adrenal and for the chorionepithelioma and hydatidiform mole. The cancer cell is not a foreign cell to its host and has no specific antigenic character in the serological sense. Reactions to cancer at the early curable stage may unfortunately be entirely silent symptomatically.

2. *Malignancy*.—With causation excluded, we deny ourselves definition of malignancy by means of "*the*" cause, and by "*the*" cause I mean the *invariable* antecedent. Definition of malignancy must be by way of description, that known as "substantial" or "essential" defining (*definitio substantialis*), which attempts to answer the question of "What is it?" by setting out what sort of thing it is ("quale sit?"). Our definition of tumours and of malignancy still dates back at least to Virchow's epoch-making conception of them as histogenetic. At this point, already I declare my adherence to the doctrine of "The Essential Similarity of Innocent and Malignant Tumours," and to that which declares: "Gradations occur between the slowest and fastest growing tumours." I should go even further and suggest "The Essential Similarity of Tumour and Malformation," the close connection between dysembryonic or dysontogenetic processes and tumour formation. I should instance the pigmented mole or macula and the angioma as cases in point. Combine these two statements of Cathcart (1907) and Mallory (1914) with all that they imply and they amount to this, that the papillomas, adenomas, fibromas and chondromas have their malignant counterparts. These are named examples of new growths which are regarded as benign because they grow slowly and show mature characters of differentiation to adult structure and function. Mention of the term "differentiation" makes it possible to point out the unsuitability of the term "dedifferentiation." That suggests a backward or downward descent, whereas malignancy is not a descent at any time; still less ought we to speak of malignant degeneration. The tendency of the new growth, if given time, is upward to differentiation. One of the main features, nevertheless, of malignancy, or greater malignancy, is rapidity of growth with failure to ascend in the maturation scale—"anaplasia" (*ἀνά* without, *πλάσσειν* to form)—as it was named by von Hansemann (1902). The new growth may, however, take a wrong turning and develop, differentiate, according to one of the atypical potentialities for the particular tissue. A metaplasia, instead of an orthoplasia, results. That is not a phenomenon specific of malignancy. The differentiated cell—squamous, mucous, fibrous, endothelial, has ended its career. It cannot continue to divide, and is of little further importance in contributing to essential malignancy. The degree of differentiation,

however, has its own importance as a clue to rate of growth. It forms the basis of "grading" or malignancy, *i.e.* grading of rate of uncontrolled growth. It is also better protected and therefore presumably more radioresistant than the naked or embryonic stem cell or cell in mitosis. There is some indication, however, that well-differentiated tumours may be more satisfactorily treated by irradiation than the rapidly disappearing, but inevitably recurring anaplastic growths (Donaldson, Spear and Glücksmann, 1944). Perhaps this relates to their small complement of undifferentiated tumour cells.

So far we have not defined malignancy, even by the method of description; nor am I suggesting that evasive action in diagnosis may be taken by claiming a fundamental identity of benign and malignant tumours. The features which distinguish the malignant new growth and suffice in their totality, yes! in much less than their totality for the diagnosis are: the useless and disorderly tendency to enlarge, persist, infiltrate, destroy, recur and disseminate. Cytological characters, such as a macronucleolus, hyperchromatism, polymorphism, etc., may contribute. Some of these characters are clinical and should be communicated to the pathologist; some are late, and may be so late as not to require the services of the pathologist. This is the case, for example, with metastasis, if it is extensive. And yet there are pathologists who maintain that metastasis alone constitutes proof positive of malignancy. I should not subscribe to that extreme view. What I do emphasise, however, is that recurrence does not represent malignancy. It may mean an incomplete removal with regrowth, or it may mean an entire rebirth, say in the case of papillomatosis of the bladder. Enlargement, again, is proliferation for the pathologist, sometimes with microscopic evidence of that fact in the number of mitoses present. Here, too, mitoses are not alone sufficient evidence of malignancy. I have, again and again, been surprised at the comparative absence of mitoses in the tumour section, although I may be fully prepared to diagnose it categorically as malignant. I have wondered whether this is due to the smallness of my sample, which is merely the thinnest of plane slices out of a comparatively large volume or whether, perhaps, some completion of cell division may continue after somatic death, with no fresh development of mitotic figures. This latter supposition is very hypothetical and could not apply to fixed biopsy specimens.

Much may be learnt histologically of the early development and character of a tumour even at advanced stages. The tumour is, we assume, advancing, and the process of development may be well studied at the perimeter. Scientific interest as well as diagnostic importance lies especially in this region, even in the case of the most obvious types of tumour. At the periphery we see the malignant development in operation or, as the case may be, judge of the benign character. Here we have the early stages of development.

With declaration of qualified adherence to the doctrines of relative malignancy, similarity of benign and malignant tumours and of

gradation in the rates of tumour growth, it might be expected that I should reject the idea of a specific cancer cell and be very willing to adopt the concept of a precancerous condition. It is to be remembered, however, that I have condemned the idea of dedifferentiation, and may here state that I consider tumours, and most of all malignant tumours, to arise always in the undifferentiated, undetermined, residual, replacement or resting tissue cell. A degree of latency (Strangeways, 1924) may commonly pertain to these cells. I subscribe to that extent to a modified Cohnheim "residue" theory. As a morphologist in daily practice, it has, however, been to me a constant difficulty to recognise the specific cancer cell. Virchow considered that it was impossible to recognise a tumour cell under the microscope. That cancer cells have certain recognisable features I fully admit—the hyperchromatism, the mitotic activity, the cell enlargement, the disappearance of cell products (mucin), the alteration of cytoplasmic staining the macronucleolus and so on—but they are not invariable. Cell degeneration and cell death are often notable changes, but these are evidence that growth has outstripped nutrition, and that is not necessarily malignancy. Agonal and atypical mitosis also is not necessarily the mitosis only of malignant growth, but is a useful clue. I come back, therefore, to the affirmation that the microscopic diagnosis of cancer is mainly and finally by tissue pattern and not from single cells. The invasive pattern is perhaps the most certain guide to malignancy. "Malignant" includes invasiveness without metastasis according to the recent Provisional Classification of Diseases by The Medical Research Council (1944). Ability of cancer tissues to continue to grow as tumour explant and transplant and the ability of a type cell to grow in subculture for generation after generation with maintenance of its characters may be admitted as argument of specificity. I have, however, seldom been able to recognise the cancer cell with satisfying certainty in, for example, pleural or peritoneal fluids, even where cancer is known to exist. I feel assailed, nevertheless, by the cogency of arguments now for, and now against, the "cancer cell." At one time I thought that the gradation I seemed to see microscopically in intestinal carcinoma at the edges of the growth was evidence of a new extending and gradation process, which was not merely the continued outgrowth of the original. In these same cases, however, one was struck also by the sharpness and suddenness of separation of the tumour from the normal, very normal, mucosa. The *carcinoma in situ*, whether intraepidermal (intralepidic) or intraductal, is another microscopic phenomenon which should have bearing on the subject, but that again might be countered by reference to the fertilised ovum cell and its marvellous growth expansion and development into well-formed tissues; to the phenomenon of eroded *cervix uteri*, or to the skin ulcer where a band of reproduced epithelial cells, very similar to the original layer, has been formed from a few diminutive groups of cells or by ingrowth from the margins. I do feel drawn when I see these "*in situ*" carcinomas toward the contact theory

which conceives of the transmission of a cancer promoting stimulus to the adjacent, as yet non-cancerous, epithelium. The present-day embryogenetic doctrines of induction, organiser, evocation and determination might help to restore the status of this much-scorned theory, actually by reference to the fertilised ovum and its progressive development, as an example of contact effect. It is better, therefore, in discussion on the " cancer cell " to preserve a fluid state of mind, to leave it as possibly due to gene mutation, virus infection or the action of chemical carcinogen, and even to keep in mind the possibility that gene, virus and chemical carcinogen may be one and the same agency.

" Precancerous " is not a term which I ever use. At the back of that obstinate avoidance, I fancy, is the feeling that the cancer cell is truly cancerous from the outset; that it has come about by the passing over of stem, residue or replacement cells, already possessed of proliferative growth potentiality; that it need not negative the continuation of this happening in neighbouring stem cells, and that if used at all it is, meanwhile, only a compromise term. Transformation of normal precursor cells of fibroblast type in cultures to the sarcomatous type seems to have been accomplished (Earle, 1943).

One more word and I shall finish with the discussion of malignancy. How is it, you may say, that pathologists can differ so decidedly on a particular case of malignancy? I should consider this as probably due to the weight that the individual pathologist accords to clinical, operative, macroscopic, radiological, statistical and microscopic features respectively. It is a common saying among pathologists, and is supported by high authority (Ewing, 1933), that if microscopically there is doubt as to the cancerous nature of the section, the microscopist may feel so far certain that it is probably *not* malignant. That reminder is from time to time quite salutary.

One detail which I must not omit is the diagnosis of " grade " of malignancy. It is not an overstatement that this aspect of diagnosis has always presented itself to the oncologist: anaplasia, mitotic activity, wild abnormality and hyperchromatism, polymorphism of cells, non-differentiation, these and others have always been considered and should be considered still. I am not fond of allotting a definite grade of malignancy in ordinary routine reporting. It seems to me too complex to give it a precise figure value, and is compounded of so many important factors that it should be a final assessment by the clinician. It is based for the microscopist essentially on the degree of differentiation to normal or functional pattern, and this pattern should certainly enter into description, but the portion of tissue used by the histologist is extremely minute by comparison with the total volume, and it is risky to assume entire uniformity of character throughout a tumour. A formula proposed for assessment of grade of malignancy with some fifteen or twenty factors is itself an example of the complexity of the decision.

To be continued

NEW BOOKS

Fundamentals of Psychiatry. By E. A. STRECKER, M.D., SC.D., F.A.C.P. Pp. 192. London: Medical Publications Ltd. 1944. Price 12s. 6d.

Psychiatry is a social as well as a medical science. The strain of war-time conditions shows up more than ever the importance of the mind in the general health of the body. The author believes that every medical man should acquire at least a minimum of psychiatric information and skill, and that it is a matter of great urgency that a workable knowledge of psychiatry be made available. In the hope of supplying briefly and concisely this need, he has written this small handbook. Beginning with a short account of the historical background of the subject, Dr Strecker discusses etiology, classification and methods of examination, then passes to a consideration of the various major disorders. The book is extremely well written, and unlike so many other publications on this subject can quite easily be understood by the non-specialist. It is a thoroughly practical book and should be of the greatest assistance to the busy doctor in general practice.

Diagnostic Methods in Veterinary Medicine. By G. F. BODDIE, B.SC., M.R.C.V.S. Pp. viii+328, with 31 figures. Edinburgh: Oliver and Boyd Ltd. 1944. Price 15s. net.

IN veterinary diagnosis there are certain inherent difficulties that are usually absent in the case of human patients, and much more depends on the veterinary's powers of observation. No direct complaint is forthcoming, and for a history dependence has to be placed on the statements of the owner or attendant who may or may not be helpful. Diagnostic ability depends on an intimate acquaintance with the appearance and behaviour of animals in normal health and on a sound knowledge of anatomy, physiology and pathology. Given these, there are many methods available for investigating the nature of the disorder. First there is the preliminary general examination in which acute observation plays a large part, then the more detailed examination of the system probably affected; and these examinations may vary in different animals.

The greater part of this book is devoted to physical examination, then follow chapters dealing with diseases of the skin, the lymphatics and the sense organs. Tuberculin and other special tests are described and methods of urine analysis are given. There is a chapter on animal parasites and a short section on clinical bacteriology. Dr H. H. Holman of the Moredun Institute contributes a chapter on hæmatology.

The book is excellently produced and Professor Boddie is to be congratulated on his valuable contribution to veterinary medicine.

The Electrocardiogram. By L. H. SIGLER, M.D., F.A.C.P. Pp. xvi+403, with 203 figures. New York: Grune & Stratton. 1944. Price $7.50.

The author, who has had many years of teaching experience, has tried to put the electrocardiogram in its proper perspective. In the past too much has been expected of the method. It is now recognised that abnormalities in the electrocardiogram are not always synonymous with structural disease of the organ. The field of usefulness of the electrocardiogram and its limitations are now more fully understood.

The subject has been treated in a practical and concise manner. Wherever possible the anatomical and physiological basis of the changes has been fully discussed.

The book is admirably illustrated and should prove of the greatest assistance to those interested in this field of practice.

Controlled Parenthood. By R. H. BOYD, M.B., F.R.C.S.E. Pp. 64, with 13 figures. London: William Heinemann Ltd. 1944. Price 3s. 6d. net.

This little book is written by the consultant venereologist to the Essex County Hospitals to give practical information on birth control methods. The author begins by presenting eugenic reasons for contraception, and the importance of the venereal diseases. He then discusses certain physiological considerations and describes in detail the various mechanical devices available. The book is carefully written in simple language and should well serve its purpose as a practical guide for the lay public.

Physical Methods of Treatment in Psychiatry. By WILLIAM SARGANT and ELLIOT SLATER. Pp. vii+165. Edinburgh: E. & S. Livingstone. 1944. Price 8s. 6d. net.

This small book gives in convenient form a most useful discussion of the various physical methods of treatment which are being utilised in modern psychiatric work. The authors do not by any means rule out lengthier psychotherapeutic procedures, but in the first place they emphasise the importance of trying to get satisfactory results as quickly as possible, and encourage us to be persistent in our efforts. To some it may seem that the authors are too enthusiastic, but that no doubt is a fault on the right side, and the only warning one would give is that a book such as this is safer in the hands of the skilled psychiatrist than in those of the undergraduate. The book indicates a new epoch in psychiatric work.

NEW EDITIONS

Lectures on Diseases of Children. By Sir ROBERT HUTCHISON, M.D., LL.D., F.R.C.P., and A. MONCRIEFF, M.D., F.R.C.P. Ninth Edition. Pp. viii+478, with 108 illustrations. London: Edward Arnold. 1944. Price 21s. net.

The present edition of this well-known text-book has been thoroughly revised by Dr Moncrieff, who, while leaving as much as possible of the original material, has brought it up to date by including the advances of the last few years. The principal alterations will be found in relation to infections of the new-born, the treatment of diarrhœa, cœliac disease and thread-worms, the types of congenital heart disease and in an account of the Rhesus factor.

The book should continue to enjoy the confidence of the medical profession.

Aids to Psychiatry. By W. S. DAWSON, M.A., M.D., F.R.C.P. (LOND.), F.R.A.C.P., D.P.M. Fifth Edition. Pp. viii+306. London: Baillière, Tindall & Cox. 1944. Price 6s.

For the fifth edition this book has undergone an extensive revision, many sections having been rewritten. However, we do not think that it offers a sufficiently full or modern account of psychiatry, even for the undergraduate.

Hypertension. A manual for patients. By I. H. PAGE, A.B., M.D. Fourth Edition. Pp. xi+80. Distributed by Baillière, Tindall & Cox, London. 1944. Price $1.50.

The person who is suddenly told he has high blood pressure is frightened and bewildered, so the author has attempted to give the patient an insight into his illness that may spare him some of the alarm and dismay and enable him to avoid the quackery that will assail him from every side. The book is full of useful advice, easily understandable by any layman.

The author suggests that the hypertensive should stand on the bank and watch the stream of life flow by, ready to step in when aid is possible and back out when

it is impossible. This economy of effort will be richly rewarded. The book, which is published by Charles C. Thomas, is beautifully produced on a standard reminiscent of pre-war conditions.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., and S. WYARD, M.D., F.R.C.P. Sixth Edition. Pp. viii+138, with 48 illustrations. London: J. & A. Churchill. 1945. Price 16s.

The feature of this book is a series of illustrations, 45 of which are in colour. These, taken from paintings, give the findings characteristic of various disorders of the blood. Accompanying each picture is a short summary of the disease, including diagnosis and treatment. Similar short accounts are given of other disorders not illustrated.

The book has been excellently reproduced and should serve as a useful guide to those interested in haematology.

Ophthalmic Nursing. By M. H. WHITING, O.B.E., M.A., M.B., B.CH., F.R.C.S. Fourth Edition. Pp. x+133, with 56 illustrations. London: J. & A. Churchill Ltd. 1945. Price 6s. 6d.

Everyone will admit that nursing is an art which cannot be learnt from books, yet good manuals such as this are practically indispensable. This little work is based on the methods of the Moorfields Ophthalmic Hospital, and gives an excellent account of the subject. While primarily written for nurses, the book is one which the general practitioner himself might find of the greatest service.

Pathology. By J. H. DIBLE, M.B., F.R.C.P., and T. B. DAVIE, B.A., M.D., F.R.C.P. Second Edition. Pp. x+946, with 395 illustrations. London: J. & A. Churchill Ltd. 1945. Price 45s. net.

The first edition of this book was published just after the outbreak of war. The present edition, considerably revised, contains such war-time additions as crush injuries, hepatitis, shock and problems arising from blood incompatibility, and also sections on gynecological pathology and on parasites.

The authors have produced a well-balanced account of present-day pathology. The book is clearly written and excellently illustrated and should prove of value not only to the undergraduate but also to the practitioner who wishes to keep abreast of medical progress.

BOOKS RECEIVED

BLOCK, RICHARD J., PH.D., and DIANA BOLLING, B.SC. The Amino Acid Composition of Proteins and Foods. (*Charles C. Thomas, Springfield, Ill., U.S.A.* $6.50

COMROE, BERNARD I., A.B., M.D., F.A.C.P. Arthritis and Allied Conditions. Third Edition . . . . . (*Henry Kimpton, London*) 60s. net.

DONALDSON, J. K., B.SC., M.D., F.A.C.S. Surgical Disorders of the Chest. (*Henry Kimpton, London*) 33s. net.

HUTCHISON, Sir ROBERT, Bart., M.D., D.SC., LL.D., F.R.C.P. The Elements of Medical Treatment. Fourth Edition. (*John Wright & Sons Ltd., Bristol*) 10s. 6d. net.

PATERSON, DONALD, B.A., M.D., F.R.C.P. Sick Children: Diagnosis and Treatment. Fifth Edition Revised . . (*Cassell & Co. Ltd., London*) 16s.

PEARSON, WILFRED J., D.S.O., M.C., D.M., F.R.C.P., and ARTHUR G. WATKINS, B.SC., M.D., F.R.C.P. The Infant: A Handbook of Management. Third Edition . . . . . (*H. K. Lewis & Co. Ltd., London*) 4s. net.

STERN, RUDOLF A., M.D. Trauma in Internal Diseases. With Consideration of Experimental Pathology and Medicolegal Aspects. (*Grune & Stratton, New York*) —

TREDGOLD, A. F., M.D., F.R.C.P., F.R.S.E. Manual of Psychological Medicine. Second Edition . . . . . (*Baillière, Tindall & Cox, London*) 18s.

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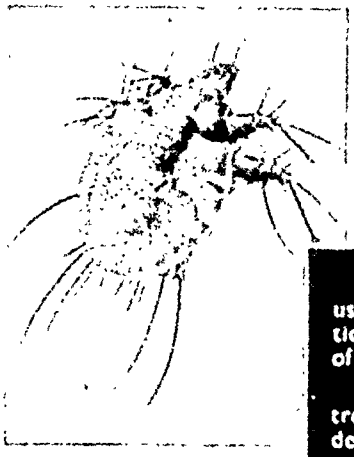

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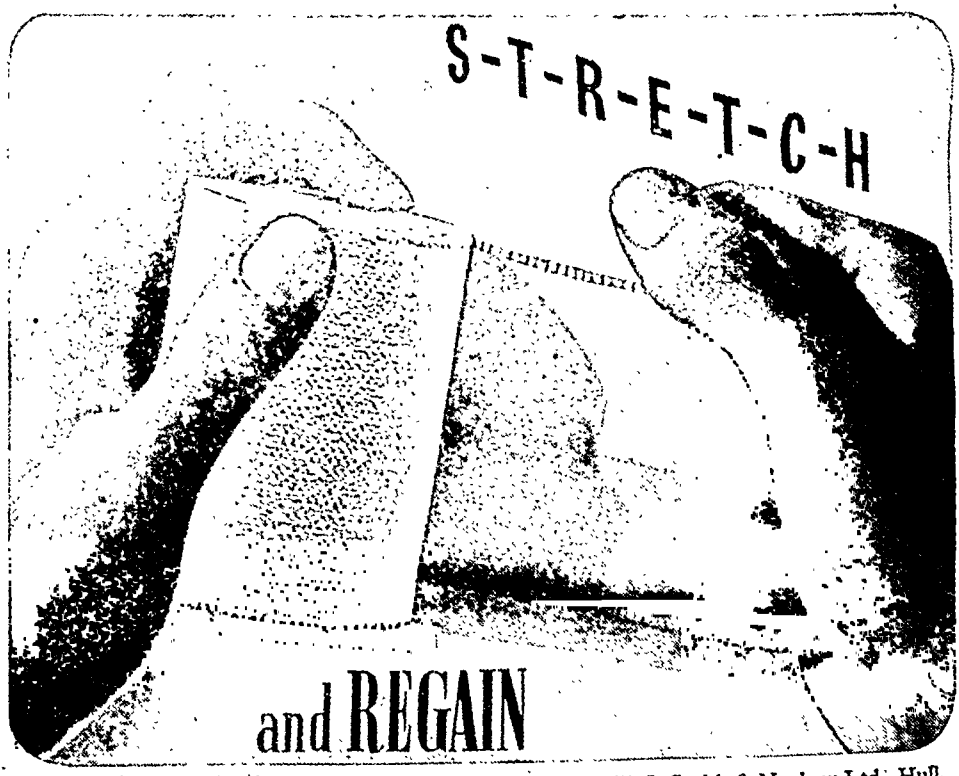

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Edinburgh Medical Journal

June 1945

SURGERY GOES TO WAR*

By W. G. OGILVIE, M.A., M.D., M.Ch., F.R.C.S., Hon. F.A.C.S., Hon. F.R.C.S.(C); Major-General; Consultant Surgeon, Eastern and South-eastern Commands

IN ancient times, and even a hundred years ago, the title "Surgery goes to War" would have sounded as trite as the phrase "The R.A.F. takes to the Air" would sound to-day. That it does not do so is due to the revolution that took place in this city and its suburb on the Clyde some eighty years ago. Before Lister, what we now call traumatic surgery formed the chief employment of surgeons. The armourer to repair the wounds of the soldier's casing and the surgeon to repair the wounds of his body were the chief technicians who accompanied an army in the field. The great surgeons of the past learned their art and established their reputations at the wars. Wiseman, Paré, Larrey, made the battlefield their laboratory and the tent their study, and wrote of wounds, infection and hæmorrhage. John Hunter, that great Scotsman who may be called the father of research, and who did more in a lifetime to advance surgery than any man before or since his day, accompanied the expedition to Belle Isle at the most impressionable period of his career.

With the discovery by Pasteur of the cause of infection, and the demonstration by Lister that infection could be prevented and by Macewen that it could be avoided, the centre of interest shifted from traumatic to deliberate surgery. The wounds studied by the surgeon were those of his own making. The problems of healing and infection passed into the background, and were succeeded by a search for the anatomical limits of exploration, the pathological territories open to operative reclamation. New surgeons and new surgical schools sprang up everywhere.

The staggering advances of the post-Listerian epoch have been obtained by the contributions of individuals and schools in many countries, often working at problems identical with those being investigated by neighbouring groups, and by the gradual emergence, among competing views, of those that appeared to be best. Attempts to collate experience on a large scale have been foiled by a lack of

* A Guest Lecture in Surgery delivered at the University of Edinburgh on 16th November 1944.

uniformity in outlook, in methods, in standards, and in material. Civil surgery suffers from Horner's syndrome, not that described by the eminent German, but that given by the unknown author of the nursery rhyme. The peace-time surgeon sits in his corner with the fruits of his labours, removing trophies through small incisions, with expressions of evident satisfaction at his own prowess.

War provides the supreme corrective to this attitude. It is an experiment on a grand scale which, rightly used, can give an unequivocal answer to many of the questions that have been debated between rival schools. The subjects of experiment are all of the same sex and in the prime of life, and they are all initially healthy, so that any lesion can be observed uncomplicated by the disturbing factors of debility, concomitant illness, age extremes, and the nutritional and endocrine failings, which confuse the picture in civil practice. The experiments are numerous enough to eliminate the errors inherent in a small series. The observers are as impartial as any observer can be, since no motive of private or corporate advancement enters to warp their judgment, and a series of different observers study each case in turn. The whole experiment is helped by an administration whose aim is to promote efficiency and to help any investigation which will lead to greater efficiency in the future. There is a record system, utilitarian in origin, but of the greatest value scientifically. And the whole experiment is conducted in the spirit of a country in arms, that mass call to united effort and the suppression of personal ambition that relieves war of much of its sordidness.

It is often said that war surgery is merely a return to the crude experiences of its early history. This view is taken too often by the governing bodies of teaching centres. In assessing the capacities and planning the future of their younger graduates, they are apt to assume that their more brilliant students, who left junior appointments at the beginning of the war to serve with the colours, have been wasting their time wallowing in blood and chopping off limbs, with no stimulus to think, no opportunity to read, and no inclination to develop that critical and inquiring outlook which is the hallmark of the scientific spirit. They turn instinctively to those who have remained behind in the atmosphere of the laboratory, the lecture theatre and the operating room.

War may bring a reversion to the primitive problems of surgery, but is the work, therefore, less scientific or less valuable? It were truer to say that war brings a return to the foundations of surgery; and just as no nation can be great which has no pride in its history, so no art or science can remain healthy or progressive which does not from time to time review the foundations of its structure. The basis of surgery is the treatment of wounds and injuries, for even the most delicate operation of the super-specialist, perfected by yearly improvement and daily repetition into a work of fine art, is nevertheless an injury, a wound which must heal. In treating the wounded, the war

surgeon is learning the art of his profession, the capacity to assess surely, decide quickly and act confidently, the readiness to subject his own interests to those of the patient, the ability to work as a member of a team for the common good. In observing the reaction of the body to injury he is returning to the groundwork of all surgical science. And in studying these processes with careful precision, recording what he observes and not what he is told should or does happen, in applying to each method that he uses, the old and accepted or the new and untried, the same impartial judgment, he is conducting research in the highest sense. For research means inquiry, and inquiry into the limits of the known demands no less industry, no less discrimination, no less originality than inquiry into the unknown. When we pause to switch the torch of investigation, which has been turned solely into the darkness ahead, to light the path behind and the land on each side of us, we learn not only of the way we have come and the place where we stand; we learn more of where we are going and what is the best way to get there.

The fundamental lesson of this war is a reaffirmation of the vitalistic faith, the rediscovery and amplification of what was learned in the last war, which in turn was a revival of the outlook of surgeons in previous wars, indeed of all thinking surgeons since time began. It is a belief that the chief duty of the surgeon is to study Nature, to find out the processes by which she fights infection and effects repair, to help them, to imitate them when they are lacking, above all, not to hinder them by meddlesome interference. This was the outlook of Hilton, of Hunter, of Paré, of the Salernian school, of Hippocrates. But it was lost, or rather overlain, in the tremendously eventful years that followed Pasteur's discovery and Lister's practice.

Before the invention of the compound microscope, which was a prerequisite to the discovery of bacteria, surgeons were necessarily limited to the study of the processes of resistance of the body. They realised that to the healthy all things are healthy; that a wound in a robust countryman will heal, while a similar one in an old man or a sick man will suppurate. But Lister's disciples, following the bacterial theory with the fanatic enthusiasm and pure faith of the Communist or the Nazi, who know only one good and one enemy, lost sight of this direct outlook. They forsook the bedside for the laboratory and the operating theatre. They were crusaders, vowed to rescue mankind from the bacterial hordes that threatened to engulf him. Sepsis was a simple matter of the entry of germs into a wound; asepsis was the avoidance of germs; antisepsis was the killing of germs that had arrived. They did not sufficiently realise that the chemicals they employed were not so much antiseptic as antivital, that they damaged the defence mechanism as well as the invader.

The first world war came as a sudden shock to upset the complacency of the theorists. Antiseptics that gave a high coefficient in the laboratories, and that seemed to work wonders in the wards, were

powerless in face of the contaminated wounds and massive infections that were seen for the first time by the surgeons who had to treat them. By bitter experience it was learned that in infection the soil is no less important than the seed; that pathogenic organisms can usually be killed by the healthy tissues of a healthy patient; on the other hand that organisms which are barely pathogenic in normal circumstances can cause fulminating gangrene when planted in large numbers in devitalised tissues, or in a patient whose resistance has been sapped by hæmorrhage, exhaustion, exposure, thirst or concomitant illness.

The school of surgery that was founded on the battlefields, the outlook that seeks to favour the powers of natural resistance and to work with and through them by gentle handling, removal of all dead tissues, accurate hæmostasis, and the obliteration of all dead spaces, has dominated surgery between the two world wars; indeed the creed of Ambroise Paré, "I dressed him but God cured him," has become that of modern medicine in the wide sense that the maintenance of health, the resistance to disease and infection and the repair of injury are the normal concern of mechanisms that have been developed through ages of evolution and are present in every healthy individual, and that the first duty of the physician is to maintain that health at all times, and to work with and through those mechanisms when it is impaired. The recognition that in many diseases such as poliomyelitis and epidemic jaundice the whole population is probably exposed to infection, but only a few individuals who show a diminished resistance succumb, exemplifies the new conception of infection that is arising. The care that is now devoted to the pre-operative "tuning up" of patients, the detailed analysis of their circulatory and metabolic reactions that is made during the operation, and the fervour with which their needs are assessed and met afterwards, shows that the reaction to trauma is regarded in the same vitalistic way. Rehabilitation is more than a catchword; it is one expression of the new ideal in medicine foreshadowed in the White Paper which aims, not merely to restore the sick to where they were before illness overtook them, but to raise every citizen to the highest state of health of which he is capable.

This war, then, found surgery fully prepared for the treatment of wounds, conversant with the failures and lessons of the last war and determined to avoid the first and apply the second. Four developments in the inter-war period had modified, without altering, the fundamentally Hunterian trend of that outlook.

The first was the recognition of the frequence and danger of cross-infection in wounds, particularly by streptococci. The bacterial flora of a wound was formerly thought to be that introduced at the time of infliction. Towards the close of the last war it was shown that the incidence of streptococcal infection increased rapidly during the progress of patients from front line to base. With the separation of streptococci into types it has been possible to prove cross-infection, and to trace the patient or attendant from whom the infection has

armies sprung from the soil

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arisen and the route by which it has been carried. Precautions to prevent such infection during operations and ward dressings have been adopted in all military hospitals.

The second was the discovery, in the sulphonamide group of drugs, of a new principle in antisepsis. Former antiseptics were all harmful in some way to living cells, and though drugs with an almost specific action on certain bacteria, and groups with a powerful antiseptic and little toxic action, such as the acridines, had been discovered, the ideal substance, lethal to bacteria and harmless to the host, had not been invented. The sulphonamides seemed, for the first time, to offer such action.

The third was the perfection of the methods of blood transfusion, and the transformation of a method, which started in the war as a life-saving expedient, into a routine procedure in major surgery.

The fourth was a wide acceptance of the closed plaster method, limited to the French in the first world war, popularised by Winnett Orr in the intervening years, and applied on the universal scale to the war wounds of the Spanish civil war by Trueta, as the most successful way of treating lacerated and contaminated wounds.

This then is the aim, and these are the weapons with which surgery went to war. What has been achieved? In general it can be said that the wounded soldier of to-day has twice the chance of surviving that he had in the last war, and a still greater chance of surviving with useful function. Some figures, taken over a long enough period and from enough cases to eliminate the element of chance, may be quoted :—

Penetrating head injuries . .	Mortality 17 per cent.
Penetrating chest wounds . .	„ 13 „
Penetrating abdominal wounds .	„ 30 „
Thoraco-abdominal wounds . .	„ 50 „
Compound fractures of the femur .	„ 7 „

In comparing these results with those of the last war, it must be remembered that they represent a more severe type of case. The doubled recovery rate of to-day is in patients of whom at least 20 per cent. are so seriously wounded that they would then have been numbered among the killed.

This improvement is due in the main to better surgery, but not at all to better surgeons. I yield to none in my admiration of the forward surgeons in this war. They have shown skill, initiative, devotion, courage, and mere physical doggedness to a degree that those who have not seen them at work can hardly believe. But to suggest that they rival in any way that brilliant band who worked in the C.C.Ss. behind the Flanders front in 1917 and 1918, and set a standard to equal which is the highest aim of any war surgeon, would be absurd. Their work is excellent. Their results exel those of their predecessors because they are working on better materials and with better tools.

That the soldier of to-day is better human material than his father cannot be proved, but will be denied by few. He has enjoyed a quarter

of a century of better social, economic and nutritional conditions, and in the army he has been trained to the highest pitch of fitness of which his frame is capable. He has been called to face many hardships, but seldom has he been exposed for weeks to mud and wet, short of water and sleep, and subjected to bombardment day and night. His natural resistance to injury and sepsis appears to be correspondingly greater. Wounds in men who have lain out for days without any attention are often found to be remarkably free from serious infection. Gas gangrene, in the same terrain and with weapons that are on the whole more destructive, is very much less often encountered than in the last war.

Smoother transport, earlier and more thorough resuscitation, and the use of chemotherapy, all combine to make the surgeon's task in the forward centres an easier and more hopeful one. At the operation itself the importance of modern anæsthesia can hardly be over-emphasised. Men so severely wounded that they will die from infection if their wounds are not excised, are in danger of succumbing to shock after operation and to chest complications later if they are anæsthetised by any of the older methods of inhalation anæsthesias; such a well-chosen anæsthetic skilfully administered is the deciding factor in survival. The less seriously wounded are sent from the theatre to an evacuation ward or tent where skilled supervision of the recovery phases is impossible; for them the value of pentothal, which abolishes post-operative vomiting and allows full recovery by the time the journey is due, can be appreciated.

That new methods rather than greater skill are the most important factors in giving the improved results of the surgery of this war can be realised if we consider penetrating wounds of the abdomen. At the beginning of the last war these wounds were considered to have a better chance if they were not operated on. After Cuthbert Wallace had reversed this policy, the mortality of abdominal operations was, nevertheless, so appalling that it was considered advisable to establish advanced abdominal centres to which such injuries were segregated. These were staffed by men who to-day hold leading positions in surgery throughout the country. The figures of the last war are therefore the figures of surgeons well above the average. Further, they are selected figures, for all that were published were those of individual surgeons, or of specialist groups, and it was never possible to analyse a large unselected series which contained the good and the bad, the lucky and the unlucky, the picked cases with the desperate chances, as has been done repeatedly in this war. Then, too, "evacuation to the base" was accepted as a criterion of recovery; it is now known that a mortality so assessed is about 10 per cent. too low. It can be said quite fairly that the death-rate of abdominal wounds in the last war was at least 60 per cent. In this war it was under 40 per cent. in the Western Desert, where conditions for operating and for after-care were infinitely worse than they were on any front in 1918. When

conditions improved, when the wounded could be brought smoothly and within a reasonable time to a well-equipped operating centre with beds and nurses, the death-rate has been from 30 to 32 per cent. In the fighting in Europe it has remained around this figure month after month in spite of the fluctuating nature of the fighting and the appalling conditions under which some of the surgeons were working.

Only one advance in operative technique can be cited as having contributed to this halved mortality, the practice of exteriorisation of all colon wounds. These wounds still show a mortality above the average, but one about two-thirds of that in the last war.

	This War.	*Last War.*
Colon alone	40 per cent.	65 per cent.
Small intestine and colon	55 „	75 „

The methods which have made the difference are accessory, rather than operative. Death after abdominal wounds, as after all others, is due to hæmorrhage, shock or infection, which in the abdomen means peritonitis. To combat the first two we have the resuscitation service which has already been alluded to; to combat peritonitis, which is fatal less from the infection itself than from the ileus to which it gives rise, we have the methods of continuous intravenous administration of fluids, and continuous gastric suction. It is still not realised by many how new these methods are. Transfusion was known and practised between the two wars; the rapid and complete replenishment of the circulatory volume both quantitatively and qualitatively which resuscitation implies to-day is largely due to the teaching and example of Lieut.-Colonel G. H. Buttle, and was first practised in the Western Desert only two years ago. Continuous intravenous medication was first advocated by Matas and Hendon in 1926, and continuous gastric suction was used by several surgeons working independently a few years before that date, but the practice of using both in all penetrating injuries of the abdomen in order to anticipate rather than to treat ileus was again first introduced in the Middle East in 1942, following the example of Major Giblin of the Australian Medical Corps.

But it is in the surgery of flesh wounds, the largest and at the same time the most important part of the military surgeon's work, that the lessons of this war can be appreciated and the progress that has been made can be assessed.

At the beginning of the war the value of prophylactic wound excision within the grace period was fully accepted, but it was also considered that after this period, when any of the clinical signs of infection were present, surgery must be limited to the barest life-saving measures: the arrest of hæmorrhage, the removal of foreign bodies and obviously dead tissues, the provision of free drainage, and the immobilisation of injured parts. These views prevailed during the phase of the phoney war and the brief campaign in France. The one lesson that was learnt during this phase was that the primary

suture of war wounds, even those received within a few hours and excised with the anatomical completeness of a cancer dissection, was fraught with the gravest danger unless the surgeon was able to keep the patient under his personal and constant supervision till healing was complete. This lesson, which cannot be cited as an advance but rather as the correction of a heresy, is still insufficiently mastered. Even within the last month wounds have gone septic, limbs have been amputated, and lives have been lost owing to the suture of wounds by surgeons too ignorant to know and too complacent to learn.

After the fall of Dunkirk, Europe ceased to be a combat zone, and for three years the school of war surgery, and the trial ground for new methods, was transferred to Africa. Here, as in all warfare, the problems and their solutions were modified by local conditions. These were the huge distances, the rapidity of movement and the fluidity of line inherent in modern mechanised warfare, the difficulty of supplies, and the relative sterility of the soil. Surgery was done by small units whose extreme mobility limited their supplies to bare necessities, and whose patients must usually be sent after operation on a long and rigorous journey through unknown hands to an unknown destination.

Surgical practice began where it had stood at the time of Dunkirk. The standard treatment was the excision of early and the drainage of late wounds, the covering of excised surfaces and the maintenance of drainage by vaseline gauze, and enclosure of the limb in an unpadded plaster case. Two accessory measures, the sulphonamides and resuscitation, were being explored for the first time on a large scale.

When the war in Europe shut down, the power of the sulphonamides to prevent infection had been proved in the laboratory, but no firm conclusion of their value in war surgery had yet been reached. In Middle East it soon became apparent that men who had been given sulphonamides, even in irregular quantities, arrived at the base in better condition than the rest. By the institution of a sulphonamide label and twice-daily dosage, it became possible to assure that every man ordered the drugs received them from the time of leaving the field ambulance to his arrival at the base. With this regime, the great majority of wounds, even those that had received no surgical treatment, arrived at the base clinically clean. This was particularly observed in head injuries which, from Alamein till the fall of Tripoli, were flown back to Cairo for operation. All were given sulphonamides from the time of wounding and during the journey, and in the great majority it was possible to operate and close the scalp wound, even up to six days, with primary union in about 90 per cent.

The use of blood and plasma in forward surgery was well established in the campaigns in France and Norway. However ill we were prepared for this war, however slow we may have been in producing effective weapons, we may pride ourselves that the British Army Transfusion Service, under Brigadier Whitby, had, at the outbreak of war, devised an organisation for the collection and manufacture of body fluids,

for their distribution to the fighting forces, and for their administration in the field, so perfect that it has been enlarged and reproduced in many countries, but modified in detail only. We may also claim that in our field transfusion service we have a means of resuscitation and of treating hæmorrhage and shock far better than any other army possesses or has possessed. But in 1940 this new weapon for the fight behind the lines was still being handled gingerly and used with caution. It was still felt that the safe rate for intravenous replenishment was about one pint in four hours, and that a rate more than double of this might embarrass the circulatory system. It was also felt that in most cases of shock and hæmorrhage plasma was safer than blood, more certainly sterile, more free from reaction, more easily administered and flowing more freely.

In the Middle East blood was used more and more, first tentatively, then with conviction, finally with the enthusiasm of the convert who has seen the light. It was found that no blood loss, however catastrophic, need be fatal if the injury from which blood is being lost can be repaired and if the lost blood can be replaced sufficiently early and rapidly with blood. It was learned that after lesser hæmorrhages a man can only be brought to the best state his injuries will allow if his circulatory loss is made up, not merely in volume but in cell-content; that with plasma alone his blood pressure may be restored, but he cannot be made safe for surgery or fit to fight infection. It was learned that the only satisfactory antiseptic against anærobes is oxygen, and the only satisfactory applicator of oxygen is the erythrocyte; that men whose wounds have been excised early and conscientiously and whose hæmoglobin has been brought up to 100 per cent. do not get gas gangrene. Finally, a standard was arrived at, that in a surgical group ten miles from the line, 25 per cent. of the casualties would need resuscitation and each would need an average of 3 pints; twenty miles back 10 per cent. would need resuscitation, the same amount, pints, being required for each. In each group the proportion was pints of blood to 1 of plasma, and in a battle it was found that roughly 0 pints of blood to 10 of plasma were required for 100 casualties.

These conclusions from Middle East have been criticised on the rounds that reactions and even deaths are said to have followed the se of whole blood; but in the hands of an experienced transfusion fficer, whose ocular assessment of the quality of a bottle is almost nfallible, they should not occur. It will be tragic if the blood which ne soldier needs and his comrades at the base and in the factories are nly too glad to give, is denied him on grounds of theory.

The lessons of three years' fighting in Africa may be summarised s follows:—

Firstly, that good surgery must be done as far forward as possible. f it is too good, in the sense of too elaborately equipped, it will not e far enough forward, and if it is too far forward it will not be good nough. The flying surgical freelance is of very little value except as

a gesture, for the preparation and after-care of patients overshadows the operation in importance. The minimum effective surgical group is two surgical units and one field transfusion unit.

Secondly, that the extent of prophylactic excision must be related, not alone to the interval before the operation, but to the subsequent fate of the patient. Where, as in the desert campaigns, a long interval and a difficult journey lay between the forward operating centre and the base, the way to safety, however apparently complete the excision may appear to have been, lay in wide drainage, careful immobilisation, and the regular administration of sulphonamides during evacuation. When this was done, it was found that the cases treated by careful removal of obviously dead tissues and wide decompression along anatomical planes arrived in as good condition as those subjected to a more classical excision, and could be closed as soon by secondary suture.

Thirdly, that the closed plaster method of wound treatment, which had proved its worth under static conditions, is unsuitable to a war of movement. The value of the closed plaster is that it confers complete immobility to the injured part and freedom from interference to the wound. To do this it must be unpadded, and must be allowed to remain undisturbed till there are clinical indications for its removal. But an unpadded cast is highly dangerous when wounded men have to be evacuated shortly after its application over long lines where the transport is rough and supervision inadequate.

Fourthly, the treatment of burns, a major problem in a campaign where petrol was plentiful and water scarce, was brought more into line with that of wounds. The burn came to be looked on as a thermal wound, requiring as other wounds do, resuscitation first, surgery and chemotherapy second, and early closure third, rather than a cutaneous lesion to be treated by the paints and unguents of the dermatologist. Tanning was abandoned early and dyes soon afterwards. Early and adequate treatment of shock by infusions of plasma, a minimal cleansing under morphine alone, dressing with some sterile substance such as vaseline, sulphonamides given by mouth rather than locally, and early transference of those likely to need grafts to a plastic centre, gave the best results.

The third phase of this war, that in which we are at present engaged, began in July 1943. In that month two profoundly modifying factors appeared. First, the theatre of operations was transferred once more to Europe. This meant wet and mud instead of sand, heavily manured terrain instead of sterile soil. It also meant warfare much more static than heretofore, operating in buildings instead of tents, surgery done in organised centres instead of in small rapidly moving and poorly housed groups, the chance to sort casualties and devote groups to the study and treatment of special wounds, the ability to retain serious cases in forward units with all the amenities of a base hospital and to get the slighter wounds away down the line to their final destination within two or three days. Secondly, penicillin became available in

the combat zone, first in small quantities for trial only, later in adequate amounts.

These factors, wounds more heavily contaminated, better surgical facilities, a more powerful bacteriostatic, and smooth evacuation have produced a profound modification of surgical policy towards soft tissue wounds.

Large flesh wounds, large not in surface extent but in the volume of devitalised muscle they contain, present a special problem. The shock that accompanies them is very resistant to treatment; indeed, the condition of the patient is often found to deteriorate progressively in spite of transfusion till the wound is excised or the limb amputated. The factor of "toxic absorption" from damaged muscle has once again been invoked; but the proof of any toxin absorption from such areas is notably lacking in any animal experiments, and indeed in clinical experience till a later period when bacterial decomposition may be expected to account for the toxæmia. It is safer to assume that shock and loss of circulatory volume are the same thing, and to explain the persistent shock in these large muscle wounds by the great capacity of the damaged tissues to absorb blood, so that the loss continues in spite of transfusion. Whatever the cause, it has been found advisable, whenever military circumstances make such a step possible, to place special teams in a forward site to operate on large lacerated wounds alone.

In other flesh wounds the practice of delayed primary suture between the third and the sixth day has been developed as an article of fixed policy. Such a plan effects a great saving in this important group of injuries, which, if properly handled, should leave no permanent disability. Early suture reduces the call on hospital beds, and the amount of dressings used, it cuts short the period of painful disability, and by lessening the amount of scar tissue, it allows earlier and better function. Where early excision is possible and early suture intended, the first operation must obviously be thorough. The limited wound toilet known as "trimming," which was the right course in wounds received late and sparsely infected, may give equal safety, but it will not allow equally early closure, only secondary suture when the autolysis of dead tissue is complete. Wound trimming has therefore been succeeded by careful excision of all dead tissues. Skin is conserved as much as possible, but all damaged fat, fascia and muscle are removed; some bacteriostatic, either a sulphonamide or penicillin, is applied with the dressing, and the limb is immobilised with a plaster slab for evacuation. Arrived at the base, the time for suture is judged by the notes of the first operation, the condition of the wound and the parts around it, and the bacteriological report, but above all by clinical appearances. At the second operation penicillin is given, either locally or parenterally, to the great majority of cases. Recent experience suggests that 80 per cent. of soft tissue wounds adequately excised in the forward areas can be closed by suture between the third and

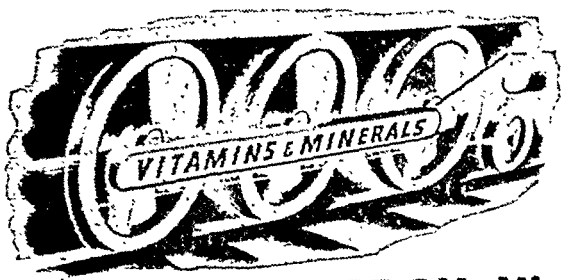
sixth day at the base, and 90 per cent. of such sutures are successful. From one army it is reported that 25,000 wounds have been closed, with primary healing in 95 per cent. Of the remainder, those which are clinically infected, those in which the skin loss can only be made good by swinging flaps or by grafting, and those in which dead tissues have not been removed completely, the majority can be closed about the third week. In this task of late closure the plastic units have played a great part in showing that with increasing experience it is possible to close even large gaps by some form of suture in preference to grafting, thus giving a covering of normal skin with its underlying fat, a better functional covering than the best of grafts.

Where early suture is the aim of the surgeon, the closed plaster method of treatment, valuable though it will always be in certain phases of warfare, is clearly unsuitable, and it can be said to be dead in the present phase of European warfare except for the treatment of gunshot fractures below the knee.

It is said that a bad workman blames his tools, but the converse, that a good workman praises his, is unfortunately seldom true. These fine results, of which we are so justly proud, have been made possible by new therapeutic agents, the sulphonamides and penicillin. These drugs are believed to act by interfering with the nutrition of the parasites and preventing their growth. Nothing can kill bacteria without harming tissues, but these new substances keep them in a state of enfeebled existence till the defences of the body annihilate them. There are thus two essentials in chemotherapy: that the agent shall get to every part where the bacteria lie, and that healthy tissues and active body fluids shall come into contact with the same bacteria. These drugs are ineffective against bacteria in dead or devitalised tissues, or in stagnant cavities such as undrained abscesses. They are useless against insusceptible organisms, and they are of little value where foreign bodies interfere with tissue resistance, or where old age or enfeeblement prevent the formation of antibodies.

Penicillin is to-day the wonder drug, the great contribution of British scientists to the allied cause and to the welfare of mankind. There is a real danger that a penicillin-minded generation may forget that the results they see are not those of penicillin, but those of Nature aided by penicillin; that if penicillin allows delayed suture of wounds with a high proportion of success, success only slightly less was obtained with sulphonamides before the advent of penicillin, and in the last war surgeons were able to close many wounds without chemotherapy.

In comparing the two methods, it must be remembered that penicillin is a luxury method, compared with which sulphonamides are cheap, stable, compact, easily administered and foolproof; conditions can easily be imagined in which the distribution and administration of penicillin in the forward areas could break down completely. Short of a complete rout, no military difficulties could interfere with the universal use of the sulphonamides. Further, there is little evidence



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from reports published by British and American surgeons that penicillin has any appreciable value in the primary treatment of wounds in the forward areas, that early suture is any easier or more successful in wounds so treated after excision, or that it has affected the incidence or mortality of gas gangrene. It has, however, done no harm, except where it had led the surgeon to neglect the proper surgical treatment of a wound or lulled him into a sense of false security. Its great value in war surgery is in four conditions :—

(1) To allow major surgery and immediate closure in circumstances of doubtful sterility in wounds where drainage must be avoided. Cranial wounds, particularly those communicating with air sinuses, joint wounds and wounds of the chest and abdomen, come into this category. Compound fractures of the long bones, which without penicillin can never be closed with safety, may in selected cases and in favourable situations be closed with penicillin therapy, with a great saving of time and improvement in function.

(2) In the treatment of established infections due to penicillin-sensitive organisms. The route by which penicillin is administered in such cases must be chosen to secure its greatest concentration at the site of infection.

(3) In the early and secondary closure of war wounds.

(4) In secondary operations on wounds which have been or still are infected. With penicillin the cleaning up and bone grafting of ununited war fractures may be antedated by months, and the eradication of septic tracks may allow a necessary nerve suture to be performed.

I have sketched the progress of surgical thought and practice in this war, but if I were to try to express the difference between the place of surgery in this war and other wars, I would say it is that surgery has not gone to war alone. If we were to jump into an aeroplane and visit an advanced surgical centre we should find a group of young men operating on the wounded, many of them specialists in one branch or another of surgery, and with them expert anæsthetists using the most modern apparatus ; in the wards we should find a physician studying a group of chest wounds, a research team making observations on shock or vascular injuries, a field transfusion officer shepherding shattered men through the valley of the shadow, a penicillin officer seeking ever to improve methods of administration, a pathologist investigating the bacterial flora of wounds. In this team spirit we have gone from good to better, till to-day we expect in the injuries of head, chest and abdomen a recovery rate twice that of the last war, in soft tissue wounds healing almost as early and as free from scar tissue as in the wounds of civil surgery. So satisfactory are the results that we may be in danger of forgetting that we are only helping the tissues to fight the battle at which they are so expert, not fighting it for them.

THE PATHOLOGY OF STATIONARY GENERAL PARALYSIS FOLLOWING TREATMENT

By E. STENGEL, M.D.Vienna, L.R.C.P. & S.Ed., L.R.F.P.S.Glas.

From the Royal Edinburgh Hospital for Mental and Nervous Diseases and the Scottish Mental Hospital Laboratory

THE success of modern therapeutic methods has provided the opportunity of studying the problem of stationary general paralysis following treatment. In the past the average general paralytic died within five years after the appearance of symptoms and only in a very small proportion, about 3 per cent. according to Rudolf (1927), did the illness extend over a longer period or become even stationary. Malaria combined with anti-syphilitic treatment arrests the paralytic process in the great majority of cases. Tryparsamide alone may achieve similar results though it is regarded as less effective than the combined treatment (Tennent, 1931). In cases which come under treatment in an early stage the prospects of a full remission are very considerable. In advanced cases complete clinical recovery only rarely ensues, but even in those cases the pathological process is usually arrested. This is borne out by the establishment of a stationary condition and by the fact that the cerebrospinal fluid returns to normal in the majority of cases. Many such cases have to remain under hospital care. The physical improvement enables them to live for a long time. Nicole (1943) has demonstrated the remarkable longevity of treated paralytics. It is not intended to deal in this article with the various clinical problems arising from the existence of that group of patients. This communication is concerned with the pathology of that condition. The pathological investigations which were carried out at the time when malaria treatment had the attraction of novelty dealt with cases who had survived the treatment for a comparatively short time only. Geary (1929) reported on histopathological findings in treated cases; the duration of life after treatment was in none of his cases longer than $2\frac{1}{2}$ years. Since then the problem has fallen into oblivion and nothing definite is known about the pathology of cases who lived 10 to 20 years after treatment. The writer has been fortunate in having the opportunity of investigating two cases of stationary paralysis who died from intercurrent illnesses 20 years following treatment. The macroscopic post-mortem examinations were carried out by Dr W. Blackwood, the histological investigations of the central nervous system by the writer himself.

CASE 1.—Mr G. A., aged 42, Private R.A.M.C., was admitted to this hospital on 30.3.1918. He had been in a War Hospital 6 months previously. He was very noisy, restless and aggressive, talking con-

stantly and expressing ideas of grandeur. He said that he owned billions of money, that he was King and his wife Queen of the Earth. He offered magnificent bribes to secure his discharge from hospital. His speech was slurring. He showed severe defects of memory and retention. There was a typical Argyll Robertson pupil and the deep reflexes were exaggerated. Otherwise he was physically healthy. WR in blood positive. Cerebro-spinal fluid : protein greatly increased, pleocytosis (no record of number of cells), gold-sol paretic curve. Only in 1922, when malaria treatment was first introduced in this hospital, the patient was inoculated and had a full course followed by treatment with neoarsphenamine. In March 1923 it was noted in the case record that the patient was quiet and did not express grandiose ideas. The WR in blood was still positive, but all the tests in the C.S.F. were completely negative. The patient's condition became stabilised. He was a good worker in the ward. He was never aggressive. There was moderate impairment of memory. The patient was contented and co-operative. His condition remained unchanged during the following years. Occasionally delusional ideas could still be elicited but he would never express them spontaneously. During the last two years of his life he became more apathetic, but according to his wife he still took an interest in family affairs and on his walks with her discussed current war events. During the last months before his death his physical condition deteriorated. He died on 21.9.1943.

Post-mortem Examination.—There was a moderate degree of emaciation. Brown atrophy of the heart; slight patchy atheroma of the aorta. No signs of syphilis of the cardio-vascular system. Early purulent bronchiolitis and basal congestion. In the lower part of the œsophagus there was a sessile carcinoma growing into the lumen and adherent to the surrounding tissues. The lymph glands related to the lesser curvature of the stomach were invaded by carcinoma.

Central Nervous System.—Brain ; weight 2 lb. 1 oz. No atrophy. Meninges and basal vessels healthy. Slight internal hydrocephalus. Macroscopically there was no ependymitis granularis. There was nothing in the macroscopical appearance of the brain to suggest general paralysis (Fig. 1). The spinal cord appeared healthy.

Microscopic Examination.—Leptomeninges : there was a slight and uncharacteristic fibrous thickening over parts of the parietal lobes ; there was no infiltration nor increase in the number of blood vessels. No endarteritis. Cortex ; Nissl stain revealed a considerable loss of nerve cells in many areas, especially in the third and fifth layers. Small groups of cells, especially of the pyramidal type, had dropped out ; the loss was more pronounced in the frontal and parietal areas and in the cornu Ammonis, less in the temporal cortex and least in the central gyri and in the occipital regions. A section from the left prefrontal area showed that, in spite of the loss of nervous elements the cytoarchitecture of the cortex was not grossly disturbed. In some

areas there were disorientated pyramidal cells. The nerve cells showed only a slight increase of intracellular lipoidal substance. No Alzheimer neurofibrillary changes nor argentophile plaques were present. There were no signs of abnormal glial reaction around the nerve cells or blood vessels. Neither the microglia (rod cells) nor the oligodendroglia showed proliferation. There was a slight increase of astrocytes in the subpial lamina, normal for the age of the patient. Myelin sections revealed a slight rarefication of the external myelinated fibres but otherwise the myelin picture was normal. There were no iron deposits, neither in the meninges nor in the adventitial or glial cells. The number of the capillaries and other blood vessels was not increased; no perivascular infiltration; vessel walls were normal.

There were no pathological changes in the basal ganglia except for an apparent slight reduction of nerve cells in the corpora striata. No ependymal proliferation. There were no pathological changes in the medulla, the cerebellum and the spinal cord.

Summary.—This was a case of general paralysis of the classical megalomanic type. The patient received malaria treatment only when clinical symptoms had been present for 5 years. The cerebrospinal fluid was found to be normal one year after treatment. Clinically the treatment had resulted in the establishment of a stationary condition. The delusions had faded out but there remained a dementia of moderate degree. The patient died from cancer of the œsophagus, having lived for more than 20 years after treatment. The brain showed macroscopically no pathological changes; microscopically a reduction of cortical nerve cells was found but there were no changes characteristic of general paralysis. The loss of cortical cells was diffuse, involving especially those areas which in general paralysis as well as in degenerative brain diseases are mainly affected.

CASE 2.—Mr A. T., aged 42, clerk, was admitted on 8.11.1923. He had been a quiet and conscientious worker until a few months prior to admission when he became careless about his work and lax about his morals, extravagant and the writer of indecent letters. He began to keep bad company and to drink to excess. Prior to his admission he had been treated by the late Dr Ford Robertson with a course of injections, probably tryparsamide. On admission he was in a mood of exaltation and expressed grandiose ideas. There was marked impairment of memory and retention. Physical examination: Argyll Robertson pupils, exaggerated knee and ankle jerks. Tremor of the tongue and facial muscles. Marked dysarthria. WR blood positive; C.S.F. WR positive, pleocytosis (number of cells not recorded), gold-sol paretic curve. In March 1924 tryparsamide treatment was instituted; the patient received 23 grm. Following treatment he improved considerably. He was better behaved and did not express delusions. As blood and cerebrospinal fluid remained positive another course of tryparsamide treatment was administered in March 1926. In August of that year the C.S.F. was found to be completely negative.

WR blood was still positive. The patient's mental condition had become stabilised. There was a mild degree of mental enfeeblement, expressing itself in childishness and lack of insight, but the general behaviour was satisfactory and there was no marked memory defect. Throughout the following years his condition remained satisfactory. He was a very useful worker, looked after the ward library, used to go out shopping for his fellow patients and his memory never seemed to fail him. He was popular with everybody. During the latter half of 1943 he lost weight and complained about general weakness. In December 1943 he suffered from respiratory distress and died on 27.12.1943, aged 61.

Post-mortem Examination.—Heart was moderately enlarged and dilated. Generalised fibrinous pericarditis. Endocardium healthy. Slight brown atrophy of the myocardium. Both ventricles somewhat hypertrophied. The aortic valve was incompetent. The aorta throughout its length and the stenosed valves of the otherwise healthy coronary vessels were involved in a syphilitic process with superimposed atheroma. There was a moderate degree of ascites and hydrothroax. Œdema of the lungs.

Central Nervous System.—Brain (Fig. 2): weight 2 lb. 1 oz. Dura healthy. Leptomeninges showed slight cloudiness over the vertex. Slight fronto-parietal gyral atrophy. Basal vessels healthy. On section the lateral ventricles showed slight enlargement. No ependymitis granularis. The spinal cord appeared healthy.

Microscopic Examination.—There was moderate fibrous thickening of the leptomeninges over some parts of the frontal and parietal lobes. No lymphocytes nor plasma cells were present, but there was a moderate increase in the number of blood vessels. No iron deposits.

Cerebral Cortex.—The same examinations were carried out as in Case 1. As far as the cyto-architecture was concerned the findings were similar to those in the first case though the nerve cell loss appeared to be slightly greater. The nervous elements had a normal appearance. There was an increase of microglial cells and astrocytes, both in the subpial lamina and in the deeper layers of the cortex. The oligodendroglia showed no proliferation. There were no signs of lipoidal breakdown and no iron deposits in the cortex. There was slight demyelinisation especially in the tangential fibres but no signs of acute myelin degeneration. The number of the small blood vessels and capillaries was moderately increased in the cortex and the adjoining white matter, especially in the fronto-parietal areas, but there was no infiltration of the adventitial spaces. A moderate proliferation of the small vessels and capillaries was also present in the corpora striata. There were nowhere signs of syphilitic or arteriosclerotic vascular changes. A slight diffuse loss of nerve cells was noticeable in the corpora striata but there were no signs of active tissue breakdown or inflammation. There was no ependymitis granularis. Cerebellum, medulla and spinal cord did not show pathological changes.

Summary.—In this case the classical picture of general paralysis developed in 1923. The patient had three courses of tryparasamide treatment. After the last course in 1926 the cerebro-spinal fluid returned to normal. A very considerable improvement ensued and the patient presented the picture of a stationary paralysis until his death in 1943. He died from heart failure resulting from syphilitic aortitis. There was slight meningeal thickening, loss of nerve cells in the cortex as in the first case, though more marked, and, in addition, a moderate increase of the microglia and of small vessels and capillaries in the cortex and the corpora striata.

Comment

In both cases the first symptoms of general paralysis had occurred at the age of 41. While in the first case malaria treatment was carried out only five years after the onset of the illness, in the second case no malaria was administered but tryparsamide treatment was instituted immediately after the onset of symptoms. In both cases treatment resulted in the arrest of the illness. From the fact that the second case reached a somewhat better level clinically no conclusions as to the greater effectiveness of the treatment employed can be drawn; Case 1 was far advanced, Case 2 in an early stage when treatment was first given. That both methods succeeded in arresting the paralytic process confirms the contention that not only malaria but also tryparsamide can achieve good results. However, in the case treated with malaria the cerebro-spinal fluid returned to normal one year after treatment, while in the case treated with tryparsamide it took three years until the findings in the cerebro-spinal fluid became negative. In neither case were pathological changes characteristic of an active paralytic process found. The anatomical condition of the brain was even more satisfactory in the first than in the second case. In the latter the loss of nerve cells was more pronounced and there were definite signs of an arrested glia proliferation, increase of vascular elements and of healed leptomeningitis. Taking into account the long duration of the illness prior to treatment in the first case, it can be assumed that the malaria treatment must have acted not only towards arresting the pathological process but also towards the disappearance of pathological reactions. Such an assumption is in keeping with the findings of Straussler and Koskinas (1925), Freeman (1927) and Ferraro (1929), who demonstrated the appearance of a temporary reactive inflammation as a result of malaria and attributed an important restitutive rôle to that specific reaction. It may be that the difference in the pathological findings in those two cases is due to the fact that tryparsamide does not produce such a reaction. At any rate, the paralytic process cannot have caused severe tissue destruction prior to treatment in either case, not even in the first patient where treatment was instituted only five years after the onset of clinical symptoms. That assumption

is in keeping with the experience that in the megalomanic type of general paralysis to which both cases belonged the prospects of treatment are more favourable than in the simply demented type, even if treatment is instituted a considerable time after the onset of symptoms. In the megalomanic type the amount of irreparable tissue destruction is said to be less than in other clinical types.

The pathological findings in those two cases of stationary paralysis following treatment are different from those in cases of spontaneous remission. Such cases, which are extremely rare, have been described by Plaut and Spielmeyer (1923), Schmidt-Kraepelin (1926) and Galbraith (1940). In most of those cases signs of an active though very mild paralytic process could still be demonstrated and in those in which such changes were absent extensive fibrous meningitis and glial scars were present. In Galbraith's case the findings in the cerebrospinal fluid were still positive at the time of death. It can be stated with certainty that in neither of the two cases presented in this article could the pathological diagnosis of a general paralysis have been made. An investigation for spirochetes could not be carried out, but it would hardly have helped in the pathological diagnosis as no spirochetes have been found in any case after treatment (Geary, 1931). Although, therefore, the pathological changes in stationary paralysis are not characteristic by themselves, the whole of the pathological picture is of a kind that does not fully correspond to any other condition of disease. The cortical changes are completely quiescent. They differ from senile or presenile diffuse cortical degenerations by the absence of characteristic senile changes and of signs of progressive tissue breakdown. The latter feature is also present in the cortex of cases with Huntington's chorea where loss of nerve cells is usually considerable. The picture of the cortex in stationary general paralysis has much in common with that found in cases with mental deficiency. The similarity of the anatomical pictures corresponds to that of the mental conditions. In fact, stationary general paralysis following treatment is a therapeutically produced artefact; progressive dementia has been changed into a state of permanent mental defect.

Conclusions

Two cases of stationary general paralysis who died from intercurrent illnesses twenty years following treatment have been reported. The first case had been treated with malaria, the second with tryparsamide. The results of the pathological examination of the central nervous system have been presented. The pathology of stationary general paralysis following treatment and its relationship to other conditions producing similar pathological changes have been discussed.

I am indebted to Professor D. K. Henderson for his advice in the preparation of this paper; to Dr W. Blackwood for putting at my disposal the macroscopic

post-mortem findings and for permission to carry out the microscopic investigations at his Laboratory; to Mr J. Sommerville, Senior Technician, for his help.

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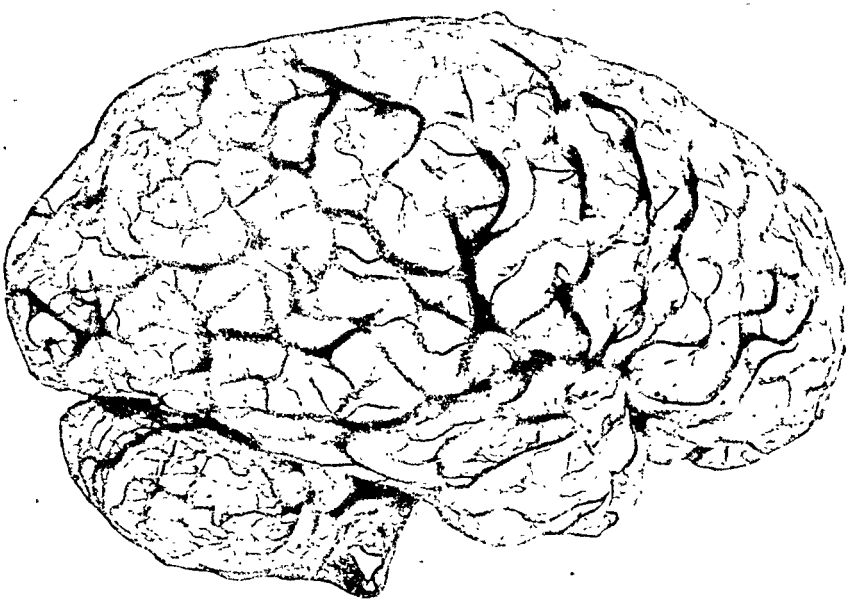


FIG. 1

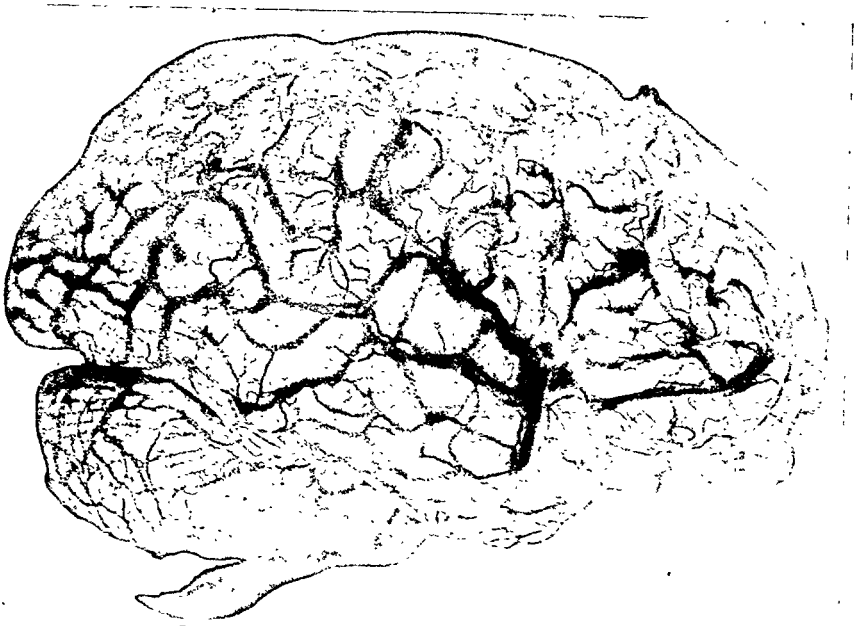
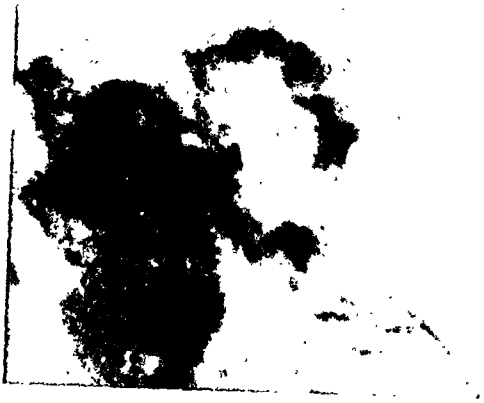


FIG. 2

PLATE I



No Erosion.

Right Ear.

PLATE II

Left Ear.

Normal.

THE "UNSAFE" EAR

By J. F. BIRRELL, M.D., F.R.C.S.Ed., Major, R.A.M.C.
Otologist to a General Hospital

IN the Army discharging ears are a constant source of worry to Medical Officers. In home units otorrhœa forms an appreciable percentage of the complaints encountered at the morning sick parade. So much so that one has received letters from Unit Medical Officers asking for guidance in the diagnosis, treatment and correct categorisation of these patients. As a result, many cases were weeded out as unfit for the Army or fit for home service only, and one anticipated that few such cases would be met with overseas.

A study of the number of cases of chronic otorrhœa seen in North Africa and Italy shows how false was this hope. It is conceivable that many patients had had a dry ear at the time of their examination on joining the Army or before embarkation, though many stated that their ear was running on one or both occasions. It is possible that the patient concealed the fact that he had aural discharge for patriotic or other reasons, in which case the examiner had not troubled to verify that the ears were normal. Yet quite a number of men had had their ears examined on one or both occasions and still were allowed overseas.

The Army lays down quite clearly the types of perforations which should exclude a man from the service, and the type which renders a soldier fit for home duties only. The dangerous perforations which make a recruit unfit for any form of service are those which indicate erosion of mastoid bone, or involvement of the attic, *i.e.* postero-marginal, postero-superior or attic perforations.

It has been shown in a previous paper [1] that the number of cases of "safe" chronic otitis media is greatly reduced overseas compared with home service, but the number of cases of "unsafe" chronic otitis media is not materially altered. At home the proportion of "safe" to "unsafe" chronic otorrhœas was roughly 5 : 2, while in North Africa and Italy the numbers have been almost identical. The reason for this is not hard to discover. Chronic otorrhœa cases of the "safe" variety show fairly large centrally situated perforations with a mucopurulent discharge that is sometimes copious. Chronic otorrhœa cases of the "unsafe" variety show small marginally situated perforations and a scanty amount of thicker secretion. They are, therefore, more difficult to diagnose, and require more care in examination if the exact site of the perforation is to be seen.

In the course of one year's work with a General Hospital in North Africa and Italy 2609 new cases were examined. Of these, 1702 had aural complaints of which chronic otitis media accounted for 396

(23·24 per cent.). Two hundred and eight of these were "unsafe" ears. Of these, 28 had polypus or granulation tissue formation in such profusion that the exact site of the perforation was not determined, and 16 had had a previous radical mastoid operation with a wet cavity. This leaves a total of 164 "unsafe" ears, of which 83 showed postero-marginal perforation, 33 had a postero-superior perforation and in the remaining 48 there was an attic perforation.

	Total Cases.	Per cent. of All Cases.	Per cent. of Aural Cases.	Per cent. of Unsafe Ears
Postero-marginal perforation	83	3·18	4·88	50·61
Postero-superior perforation	33	1·26	1·94	20·12
Attic perforation	48	1·84	2·88	29·27
Total	164	6·28	9·70	100·00

Diagnosis

There is usually a history of long-standing, and sometimes foul-smelling, aural discharge which has frequently been present since childhood, of deafness which may only be slight, and of occasional pain which is not severe.

Discharge

Of the 164 cases under discussion, 96 (58·53 per cent.) had had otorrhœa since childhood, while a further ten patients gave a history of discharging ear of 5-10 years' duration. A history of 1-4 years' aural discharge was given by 38 men, most of whom attributed the onset to some accident during their Army life—gun or shell blast, bomb explosions, blow on the ear, injury during physical training, etc. This is a perfectly understandable state of affairs, and many patients genuinely believed their own story, even when it was pointed out that such traumatic ruptures rarely affect the drum marginally. Such an accident undoubtedly aggravated the pre-existing aural condition, but never caused it. The remaining 20 cases gave a history of less than one year's duration. In the majority of these the factor which prompted the patient to report sick was an otitis externa, and the true aural condition was discovered during the treatment of the external infection.

Pain

Pain was complained of in 103 (62·80 per cent.) cases, denied in 38 (23·17 per cent.), while in 23 no notes are available. In the great majority pain was intermittent and by no means severe.

Deafness

A deficiency in hearing was admitted by 142 (86·59 per cent.) patients, denied by 14 (8·53 per cent.), while in 8 no notes have been made. One learned by experience not to question the patient about

deafness, but rather about the state of hearing. A soldier's idea of deafness is an absolute lack of hearing. The hearing loss is seldom great, and 80 per cent. of patients had an Army Hearing Standard qualifying them for Category A1. In the Army one cannot place the same reliance on tuning fork tests as one did in civilian practice. A positive result to Rinne's test does not exclude middle ear suppuration, as so many soldiers, especially gunners, have a bone conduction loss as a result of noise and concussion from gunfire.

X-rays

X-ray photographs of the mastoid processes frequently show an acellular process on the affected side, and one can sometimes see evidence of bone destruction by cholesteatoma, especially in the region of the attic (Plate I).

Postero-marginal Perforation

The postero-marginal perforation is the most common of the three types of "unsafe" perforation, being met with as frequently as the other two put together. Discharge had persisted since childhood in

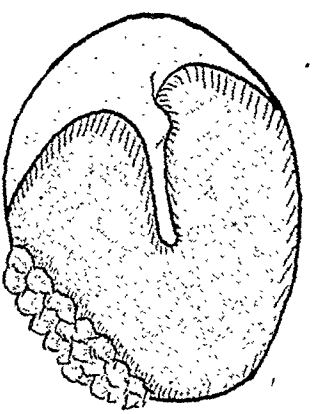


FIG. 1.—Postero-marginal granulations.

51 (61·45 per cent.) cases. Pain was complained of by 53 (63·86 per cent.) patients, and deafness by 72 (86·75 per cent.). The perforation itself is often not seen, as it is usually hidden behind a small bunch of granulations protruding from the posterior meatal wall about the level of the middle of the drum (Fig. 1). A co-existing otitis externa was found in about one-third of the cases, and this granulation tissue against an apparently normal drum is found so frequently that one might wonder whether it represented part of the external infection. This view can be discarded for three reasons—firstly, the long history of running ear and deafness in many of the cases; secondly, the X-ray evidence of chronic mastoid infection; and thirdly, what might be

Prognosis and Treatment

The danger in these perforations lies in the fact that they denote a chronic infection of the mastoid bone. Vital structures such as the dura mater, the lateral sinus or the membranous canals may be exposed by the insidious process. Any acute exacerbation may result in a meningitis, sinus thrombosis or labyrinthitis developing rapidly. That is why the Army will not admit men with such a perforation. If admitted, they should be employed in home service only.

The process is only arrested by surgery, and thus prognosis must in all cases be guarded. The only treatment is operation, either the radical or, preferably, the modified radical mastoid operation. The objects of such an operation are briefly to put the ear in a safe condition, to improve hearing, and to ensure a dry ear. A properly executed mastoid operation will result in a safe ear in every case. Hearing is improved with the modified radical mastoid operation in the vast majority of cases. A resultant dry ear depends entirely on adequate after-treatment. Many writers quote more than 80 per cent. of dry ears (Bolotow,[2] Maxwell and Richter[3]), while Hall[4] has obtained 95 per cent. dry ears in a series of 211 modified radical mastoid operations. Hall has shown the average healing time to be nine weeks, and in his series of 373 cases no death has occurred.

Summary

It has been shown that while many cases of "safe" chronic otitis media in soldiers have been stopped from service overseas, a great many "unsafe" ears have been found in North Africa and Italy. Of 1702 aural cases seen in a General Hospital E.N.T. department, 10 per cent. had conditions which should have prevented them from joining the Army.

The reason for this is that the perforations denoting chronic mastoiditis, viz. postero-marginal, postero-superior, and attic, are difficult to diagnose. The salient features of these perforations have been described and the method of spread of infection has been discussed at some length.

Brief mention has been made of the prognosis and the results to be expected from surgical treatment and adequate after-care.

I am indebted to Colonel C. H. K. Smith, O.B.E., M.C., commanding a General Hospital, for permission to publish this paper, and to Major F. Pygott, R.A.M.C., for the X-rays which illustrate it.

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ACTINOMYCOSIS *

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LADIES AND GENTLEMEN,

I choose this subject as I have had the good fortune to have admitted under my care during the War a group of cases suffering from actinomycosis. As a general surgeon I have been able to witness the difficulties that arise in the diagnosis and treatment, and have been impressed that team-work between the bacteriologist, the radio-therapist and the surgeon is essential in guiding the case to a successful recovery.

The disease in man and animals is still shrouded in mystery, largely due to the loose terminology which has grown up with the steps of discovery in its life history. Pioneers in this work have approached the problem from many angles over a period of time, with the result that several diseases associated with pus formation containing club-bearing granules have all fallen under the heading actinomycosis. As we proceed to-day we will be able to see how the past still influences the present state; for instance, a disease called woody tongue in cattle responds rapidly to treatment with potassium iodide, but we continue to believe in the use of potassium iodide in the treatment of actinomycosis in man when no rapid clinical improvement has been demonstrated, knowing full well that the causal organism, thought to be the same for both diseases in the past, has now been proved to be different in either case.

BACTERIOLOGY.—The causal organism in man is a ray fungus called *Actinomyces bovis*, and it is isolated from the lesion in areas where the tissues are softening and breaking down. To attach the term *bovis* to an organism occurring in the human body is only to lead to confusion, so I must needs take you back into the history of this disease so that a firm foundation can be laid.

Bollinger in 1877 and Perronito in 1879 described granulomatous formation with the occurrence of débris taking place in the jaws and throats of cattle. The débris contained yellow granular bodies from which a fungus was isolated, and in 1879 James Israel described a fungus isolated from a chronic empyema of man similar to that discovered by Bollinger. Harz the botanist, in 1877, examined Bollinger's specimens and saw portions of the mycelial element of an organism which he called a ray fungus or actinomyces. Oscar Israel (1884) and Bostroem (1891) found the fungus to be aerobic,

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 25th January 1923.

but, in 1891, Wolff and James Israel showed the cultures of *Actinomyces bovis* to be anaerobic. The term *Actinomyces bovis* has remained, as the organism can cause lesions in cattle as well as in man, but the commoner condition of woody tongue in cattle is due to the actinobacillus of Lignieres and Spitz. This Gram-negative aerobic bacillus has been confused with *Actinomyces bovis*, but it does not give rise to lesions in man. Now that we have elucidated one causal organism for man, I feel that we should complete the picture for the animal kingdom, by saying that infections associated with granule bearing club formations may be due to *Actinomyces bovis* causing lumpy jaw in cattle, the actinobacillus of Lignieres and Spitz causing woody tongue in cattle, and the staphylococcus causing lesions of the udder of cows and pigs, or botryomycosis in the horse.

Turning to the causal organism in man, *Actinomyces bovis*, we would now like to know what it looks like and something of its habits. Dagny Erikson in her work has given us a very clear impression of the growth of the organism. " The germinating cell elongates and in doing so may remain straight or bend at an angle. A branch develops which may elongate or produce more branches until a mycelium is formed. At the end of the fifth day the hyphæ may show fragmentation. As the colony grows older the protoplasm may form as granules in the branches, and club-shaped swellings may appear on the end of the filaments. In young active colonies the mycelium and filaments evenly stained with Gram are seen, but in older colonies or colonies growing on special media club formations may be present. The organism isolated from cattle shows shorter filaments which tend to break up, giving rise to bacillary or diphtheroid forms, and not to display the radial aspect of the typical colony of the human strain.

The formation of clubs is only found when the organism is isolated from the lesion in man and grown on media containing serum. It was thought for these reasons that club formation in tissue was a biological response of the host to invasion, but Bayne-Jones has shown that the organism can be grown on 1 per cent. glucose meat infusion agar or broth, and show club formation. I have considered the possibility that club formation is a sign of old age, and that would account for its common finding in granules extruded from the body following the process of softening.

Actinomyces bovis grows best in a state of lowered oxygen tension, therefore conditions that are almost anaerobic suit it best, and the organism is classified as a microaerophile. The filaments take up the Gram stain, and only survive when grown about body temperature. The organism is difficult to isolate and culture, and gives the bacteriologist trouble in testing its sensitivity to drugs such as penicillin, as well as when confirming the diagnosis for the clinician.

We will now pass to a description of the lesions occurring in man and after their study we will be in a position to consider how the organism was able to reach the tissues.

PATHOLOGY.—The three common sites in man are the cervico-facial region, the abdomen and the thorax.

The reaction of the tissues to invasion by the organism depends on their cellular content, thus causing the variations seen in the neck, the liver and the lung. In the neck the organism flourishes and moves in the connective tissue planes, setting up a tremendous fibroblastic reaction in comparison with the other common granulomas. This reaction gives rise to the marked induration of the tissues in the cervico-facial region and produces trismus as an early sign. The blood vessels passing through the fibrous tissue are intact in comparison with the endarteritis associated with tuberculous and syphilitic lesions, and this may account in some degree for the slow breakdown of the tissues or clinical softening of the affected area. Months may elapse before an area of softening appears, then the skin breaks down and from the sinuses formed, the typical pus is discharged containing granules, which vary from grey to green and yellow in colour. If the sinus has been present for some time, secondary infection may have taken place, or else a process of self-cure is on the way and all that is seen is a watery discharge free from granules. The granules contain the fungus and so the process of softening almost appears to be an attempt on the part of the body to extrude the offending organism like a foreign body, and the fibroblastic reaction a method of localising the trouble. In the liver the cellular element predominates over the connective tissue element with the result that there is rapid destruction of vital cells, as the fibroblastic reaction is poor, with the resultant formation of the large honeycomb abscess with comparatively thin walls. It is of interest that the organism does not permeate lymphatics, and there has been no clinical evidence of involvement of lymph glands in my group of cases or in those recorded in the literature. In actinobacillosis of cattle lymph glands are commonly involved, so it has been suggested that the organism *Actinomyces bovis* is too large to enter lymphatics and that in the case of the connective tissue planes it is spread by carriage in macrophages.

Another point of interest lies in the fact that the jaw bone is rarely involved in spite of the proximity of the lesion in a high percentage of cases. Apart from periosteal reaction my cases have shown no evidence of bone disease, but Wakely has shown sequestrum formation in a few cases. On reading the description of these cases the disease appears to be extensive and advanced, so that possibly invasion by secondary organisms would account for the bone destruction. Spread is mainly by direct invasion of tissue, but on occasion the organism erodes a vessel of the portal circulation and gets carried as an embolus to the liver, and there are cases recorded of metastases to the wall of the heart and other parts of the body through the systemic circulation.

The main pathological features of the lesion as it occurs in the human body have now been discussed, so we can try to solve the problem of the occurrence of this disease in man.

Confusion has arisen due to the fact that actinomyces have been found in cattle, on grasses and cereals, and in man, and great delay took place before the findings of the experts in veterinary surgery, botany and medicine were correlated. Bostroem in 1891 isolated *Actinomyces bovis*, but it proved to be aerobic and differed in viability and cultural characteristics from the Israel-Wolff *Actinomyces bovis*, though morphologically it had great similarity. Bostroem's organism was found on grasses and soil, and so it followed that cattle ate the grass and man sucked the straw and thus both acquired the disease. It has now been shown that no anaerobic Gram-positive hyphomycete has been recovered from the soil, grass, or grain, and that in this country citizens and farm labourers are equally affected, though in America the farm labourer is more liable to the disease. There is very little evidence that the disease can be transmitted direct from animal to man, or from man to animal, so we are left to seek an explanation elsewhere; but before we leave such fruitful ground I would remind you of Neuber's findings in which he found that anaerobic strains were often cultured from pus from living patients, while the post-mortem material yielded the aerobic variety. It has therefore been suggested that *Actinomyces bovis* may live aerobically on grasses, and anaerobically in the tissues of man and animals.

The question now arises as to how man is infected if the source from the soil is ruled out. Lord, Trevett and Emmons have isolated organisms from normal mouths of man, which correspond in morphology and growth habits with the *Actinomyces bovis* of Wolff Israel. These organisms are quite a common finding in man and therefore do not fit in with the rarity of the disease (1 in 3000 admissions in British hospitals). What are the conditions which would change a saphrophyte into a parasite? Klinger in 1912 isolated a Gram-negative cocco-bacillus associated with actinomycosis, and Colebrook in 1920 found this bacillus present in pus aspirated from 80 per cent of closed lesions in man. Colebrook was able to show that this *Actinobacillus comitans* was not the same organism of actinobacillosis as isolated by Lignieres and Spitz. Bayne-Jones described the presence of this organism in the first case in America in 1925. It is suggested that this bacillus and other organisms may produce the anaerobic conditions in which *Actinomyces bovis* can flourish as a parasite. In favour of this theory we have the fact that the common site for actinomycosis is the cervico-facial region associated with a primary infection from the mouth, the source from which saprophytic forms can be recovered, and the incidence of the age group for this disease corresponds with the period for onset of dental caries and sepsis, children being rarely affected. The dental surgeon is often blamed for the onset of the disease, and in my series of cervico-facial cases of actinomycosis 50 per cent. developed a swelling in the neck before the dental surgeon saw them, and 40 per cent. attended the dental surgeon for dental caries or sepsis, the condition of actinomycosis manifesting itself

clinically at varying intervals following dental extraction. That means that 90 per cent. of the cases required treatment for dental caries or sepsis.

The organism appears to enter the body through the intestinal tract and thus accounts for the three common sites in man. The primary lesion and the mode of spread appears to be dependent on the type of tissue encountered. In the mouth the organism appears to pierce the mucous membrane and enter the submucous coat, but there is usually very little evidence of a primary ulceration of the mucous membrane, even when the process is active in the neighbouring connective tissues, suggesting that the mucous membrane is highly resistant to the organism and heals quickly, or alternatively, that the organism does not enter the mucous membrane until disruption has taken place due either to sepsis or trauma occurring in relation to carious teeth. Some workers have suggested that the impaction of grain seeds set up the initial trauma, and thus explain away the association between the eating of grain and the occurrence of the disease. In 21 cases of cervico-facial actinomycosis at Westminster Hospital, only one case showed ulceration in the mouth and that appeared in the form of a small ulcer on the dorsum of the tongue, but induration and sinus formation had been present in the neck for six weeks. The mandible in all my cases was free from disease apart from slight sepsis or absorption of bone around carious teeth. This is in marked contrast to actinomycosis in cattle where the disease is primary in the jaw bone giving rise to suppuration, destruction and rarefaction of bone, and new bone formation at the periphery, with the result that there is marked enlargement of the bone associated with sinus and sequestrum formation.

The organism settles in the connective tissues of the neck or face in man, and the massive fibroblastic reaction gives rise to marked induration of the tissues, preventing opening of the jaw and in 3 cases causing marked chemosis of the conjunctiva of the eye, but just stopping short of invasion of the subconjunctival tissues of the eye. In 2 cases there was extensive involvement of almost the whole neck, but in neither case was respiratory distress noted. The process of spread in the connective tissues is slow but by no means uniform. Waves of activity of the causal organism will rapidly cause the brown leathery skin to become reddened and tender to touch over a wide area, and at this stage the patient may suffer severe pain associated with pyrexia. Softening usually occurs in one or more places following this wave of activity, and then pus containing sulphur granules is discharged. It has been suggested that secondary organisms are responsible for this phase, but I am inclined to regard it more in the light of a fixation abscess which has formed as the result of a battle between the tissues of the host and the causal organism, the causal organism having lost and being extruded in the form of granules along with the débris of the battlefield. The organism may spread

down the neck into the mediastinum, or up to the base of the skull, but the process is usually localised to the cervico-facial region. Lymph glands are not involved in this disease, but lymphatics may be involved in the fibroblastic reaction giving rise to œdema of the eyelids; this is well seen during the phase of activity I have just mentioned, but soon settles down again, suggesting that it is only a question of temporary pressure and not blockage of lymphatics by invasion.

The blood vessels in the tissue undergoing fibroblastic reaction remain unaffected and only on very rare occasions are they invaded, as instanced by recorded cases of metastatic lesions in the brain, heart and kidney. I have been very interested to note how the induration of the tissues due to fibroblastic reaction subsides after the organism is expelled, and the excellent results obtained to-day are due I think in a large degree to early diagnosis so that secondary organisms do not complicate the picture and give rise to permanent scar tissue.

In the abdominal form the organisms seem to invade the intestinal tract in the region of the cæcum and the appendix. The lesion is first seen as grey flat nodules in the submucous coat, and it is difficult to explain why the ilio-cæcal area should be selected for invasion. We do know that appendicitis is the commonest inflammatory lesion in the intestinal tract of man, and that fæcal concretions are commonly found in the appendix, so there is the possibility that secondary pathogenic organisms provide conditions favourable for the growth of the pathogenic *Actinomyces bovis*, and that the fæcal concretion provides the factor of trauma required to cause an abrasion in the mucosa.

The organism spreads through the bowel coat to gain the retro-peritoneal tissues and so a large mass forms in the right iliac fossa and spreads into the loin. In the course of time suppuration occurs, and sinuses form and discharge granules and débris.

The organism does not invade the peritoneal cavity, suggesting that the peritoneum like the mucosa is highly resistant to attack. Owing to a greater liability to secondary infection the rate of the spread of the disease varies in each individual. In some cases a localised mass with sinus formation forms and cure follows in a few months up to two years; in other cases there is rapid spread with large abscess formation and death ensues in one to two months. In some cases the portal circulation is invaded and the organism is carried to the liver where the fibroblastic reaction is poor and the resulting destruction of vital cells is great. Here again variations in the rate of spread occur but the issue is always fatal.

Entry to the lung may take place by two paths. One method is by aspiration of the organism from the pharynx into the bronchus, and in support of the theory I quote a case in which a carious tooth was found in the centre of an actinomycotic lung abscess.

A second path is through the mucosa of the lower œsophagus. We have seen that the mucosa rapidly heals and therefore entry could

be gained through the œsophagus and leave no evidence behind. In support of this theory we find that in some cases the first sign of thoracic actinomycosis is the pointing of an abscess on the thoracic wall at the level of the diaphragmatic attachment, which may be due to the organism having tracked from the mediastinum along the connective tissue planes between the pleura and the ribs. In two cases under my care the disease was first discovered as a case of chronic empyema, one case developing thoracic symptoms two months after operation for removal of an inflamed retro-cæcal appendix. Once the lung tissue is invaded there is so little fibroblastic reaction that the mortality is high.

DIAGNOSIS.—I will now turn to a few practical points that are of value in the diagnosis of the condition. In the cervico-facial form of the disease many weeks may go by before softening occurs in the indurated area, but when it is present the surgeon has the best opportunity of establishing the diagnosis.

The area should be incised and pus if present collected in a test tube; very often pus does not form, and one is confronted with breaking down tissue which has to be curetted out. If pus is obtained strain it through gauze. The granules obtained in the gauze should be soaked with strong NaOH on a glass slide, crushed and stained with Gram. A lobulated colony of Gram-positive mycelia is seen. Another method is to centrifuge the pus and embed the sediment in wax and stain sections with hæmatoxylin and eosin. The microscopy of the granule is what is required as it contains the mycelium with its radially arranged club-shaped filaments. Sections of invaded tissue very rarely show granules and the mycelium does not usually show club formation. Secondary infection makes isolation of the fungus a difficult matter, therefore in cases with sinus formation it is difficult to find the organism and almost impossible to culture.

In about 80 per cent. of cases of cervico-facial type, trismus is present as an early sign even though the area of induration is small. The induration in the tissues gives rise to a lumpy or nodular formation and the late softening distinguishes it from the granulomas of tuberculosis and syphilis.

In the abdominal form the spread of the mass to the retroperitoneal tissues gives rise to a swelling in the loin associated with a mass in the right iliac fossa, and that in turn gives rise to the early sign of flexion of the hip due to involvement of the ilio-psoas muscle. Actinomycosis of the lung is discovered at a late stage as it occurs in so many forms and cannot be recognised till the organism is found in the sputum or in the pus of a surface abscess.

The prognosis of the condition has altered slightly in the past fifteen years, due I think to the earlier recognition of the disease cutting down the degree of secondary infection, and to the guidance of the case by various forms of treatment based on a better knowledge of the reactions of the body to the disease.

In the cervico-facial form McKenty shows that out of 14 cases treated, 12 were cured and 2 improved. Mattson showed that out of 19 cases treated, 12 were cured and 7 improved. At University Hospital, Tennessee, out of 15 cases treated, 14 were cured and one died from generalised spread of disease. In a series of 21 cases treated at Westminster Hospital, 20 were cured and 1 improved. I have been struck by the complete disappearance of induration in cured cases, and I think it has been due to the treatment given to the patients. Out of 13 cases treated between 1940 and 1944, 12 have remained cured up to date, and one case at present has a small local recurrence. Out of 8 other cases treated between 1934 and 1939, 6 cases are cured and the remaining 2 cases were healed but have now been lost trace of. The patients in the period 1940-44 were Service cases so had to be treated as in-patients. I am able to give you some idea of the time required for treatment to be effective. The average duration was three months, the shortest period six weeks, and the longest period five months. These patients at the end of this time were healed. In a series of 23 cases at University Hospital, Tennessee, the length of time for healing varied from ten days, following discharge from hospital, to six months. All my Service cases have been able to return to full duty and only two have had recurrences, one of them cured by further treatment, and the other responding to a further course of treatment being given at the present time. In the abdominal cases the mortality is high, varying from 50 to 80 per cent., all cases with involvement of the liver leading to a fatal issue. In thoracic actinomycosis the mortality is almost 100 per cent. if the lung is involved, but Wangensteen shows in a table of 19 cases of thoracic actinomycosis collected from the literature from 1892 to 1932, that cure had taken place in all, and one patient was reported well sixteen years after treatment.

It can be seen that the prognosis is largely dependent on whether or not a vital tissue is involved, and whether it is capable of a fibroblastic reaction.

TREATMENT.—Now that we have traced the cause of this disease and observed its course in the human body, we can turn to the question of treatment. It is interesting to review the literature and note the numerous remedies advocated in this disease during the past sixty-five years, even to penicillin in 1945. The drugs used in the cure of this disease have come and gone in a manner suggesting that there was no specific remedy for the disease, so why not try the latest drug that has been discovered to be of value in the cure of other diseases. Potassium iodide has, I think, been used constantly, as it rapidly cured woody tongue in animals, a disease due to actinobacillosis and mistaken for actinomycosis by early workers.

In addition, potassium iodide was found to have a rapid curative effect on granulomas due to syphilis. The other lines of attack have been to kill the fungus, an organism of low virulence, with various

antiseptics. Pure carbolic, formalin, thymol and copper sulphate have been in turn applied to the sinuses in an attempt to sterilise them, and thymol, copper sulphate, sulphonamides and penicillin have been given by mouth or injection in the hope that they would get carried in the blood stream and destroy or inhibit the growth of the organism in the lesion.

Potassium iodide is the one drug that is universally used in the treatment of actinomycosis, so let us consider its therapeutic action, so that we can assess its value apart from its historical interest. Iodides are given by mouth in place of iodine as they are less liable to set up gastro-enteritis; when absorbed they combine with the proteins of the tissues and liberate some free iodine. In the tertiary lesions of syphilis they get carried to the necrotic tissue of the gumma and assist in early autolysis of the débris. It was thought that the free iodine liberated might kill the spirochæte, but this does not occur as iodine and iodides have no effect on the spirochæte in the primary stages of syphilis. Iodine itself has the same action as any counter-irritant, and it is possible that when it reaches the lesion of actinomycosis it may help to tip the balance in favour of the tissues by vascularising the part and increasing the leucocytic action, thereby causing early softening in the tissue and extrusion of the offending organism. Jobling and Petersen express the view that iodine neutralises the action of the agents which prevent solution and absorption of the necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which had been previously protected by the necrotic tissue. They suggest that iodine is set free in the necrotic tissue, and quote Loeb's work whereby he found that on administration of iodides to syphilitic patients the diseased softened lymph glands contained about twice as much iodine as was present in the unsoftened lymph glands. Henrici and Gardner isolated a variety of actinomyces from a case of pulmonary infection and tested the effect of potassium iodide *in vitro*. The cultures of this form of actinomyces remain extremely virulent, unlike cultures of *Actinomyces bovis*, so it was thought worthy of chemotherapeutic experiment. The growth of cultures of this organism in broth was found to be retarded, but still grew in the presence of 10 per cent. of potassium iodide in broth. Herbitz and Grondehl found that *Actinomyces bovis* was unaffected in its growth in culture media which contained concentration of potassium iodide up to 2 per cent.

Many surgeons have noted the extreme vascularity of the granulation tissue formed when the patient is treated over a long period with potassium iodide, and suggest that potassium iodide increases the formation of new blood vessels. In my experience I have not been impressed by the excess of vascularity of the tissues at the time of operation, and the clinical state has never produced the redness, heat and swelling associated with such a pathological change except in small areas where the tissue is breaking down. The

fact that iodides can be excreted through the skin as well as by other channels, and that the greater proportion of actinomycotic lesions lie under the skin must have influenced those in favour of its use in early days.

To sum up the position, I would say that we have no scientific proof that potassium iodide is of value in the treatment of this condition, but actinomycosis is classified in the group of granulomas and we do know that the granuloma of syphilis can melt away under the influence of potassium iodide. Our practical experience has not yet shown us a case undergoing rapid cure by the use of this drug, but there is a weight of evidence suggesting that softening of the lesion occurs with greater speed, and as I think softening is Nature's method of extruding the causal organism, I would continue to use potassium iodide on the grounds that it is a drug that will help to promote the rate of recovery. Many writers advocate that iodine should be taken in various forms—iodine in milk, collosal iodine, Lugol's iodine, etc.—but having tried them all I have returned to the use of potassium iodide, as no marked benefit was observed when using any of the special forms recommended. Two complications can arise when iodides are administered in large doses, iodism and depression. It is said that if iodism develops, doubling of the dose will relieve the condition. In my recent series of cases all patients were receiving potassium iodide in doses of 300-400 grs. a day, and only one case showed signs of irritation in the form of a rash. In this case the rash occurred when the dose was in the region of 90 grs. a day, so it was raised to 180 grs. a day rapidly, and the rash halted and then slowly subsided. Three patients developed severe depression, but this state occurred when they had been treated over a long period with iodides, surgery and deep X-ray therapy, and was associated with a secondary flare-up of the condition, giving rise to severe pain. In these cases all forms of treatment were stopped and the patients went on to a slow stage of healing without further treatment. I suggest that iodides should be used, but if the complication of iodism does arise the dose should be rapidly increased; if there is no response in a few days then it should be abandoned, as its effect on the actinomycotic lesion appears to be very slight.

Arsenical compounds have been used on the ground that the granuloma of syphilis responded, but no effect has been obtained in the treatment of actinomycosis. Bèvan administered copper sulphate internally and by local application with success, but other workers have not been able to substantiate his results, and so the use of many drugs is recorded in the literature. I shall confine my remarks to thymol which has recorded some success in the past and the sulphonamides and penicillin which, as the drugs of to-day, are of interest to us.

Kingery and Thynes in 1925 demonstrated that thymol had a fungicidal action in a yeast-like dermatosis occurring in fruitpickers in North-West America. In 1927 Myers experimented with 22

'POLLACCINE'

For the Prophylaxis of Hayfever

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Immunization against grass pollen toxin, the specific causative agent in hayfever, is best accomplished by a long succession of prophylactic injections commencing early in the year and continued until a few days prior to the commencement of the hayfever season.

Provided a sufficiently high dose is reached, patients previously highly sensitive to grass pollen can pass through the hayfever season with complete immunity from symptoms.

The frequency of inoculations will depend upon the time available. When injections are not commenced until late in March, a dose will have to be given every day. If treatment is delayed until May, as many as three injections daily may be necessary.

For patients who experience only mild attacks of hayfever, amelioration of the symptoms during the summer months can often be secured by far fewer inoculations than are required for the complete desensitization of severe cases.

•

'Pollaccine' is an extract of grass pollen prepared in the Laboratories of the Inoculation Department (Founder, Sir A. E. Wright, M.D., F.R.S.) of St. Mary's Hospital, London, W.2., and is considered to be the polyvalent for the pollen for all grasses.

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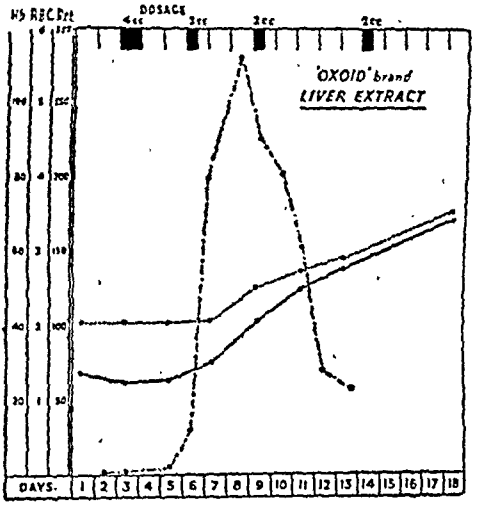

KEY TO GRAPH.

..... *Haemoglobin per cent.*
——— *Red blood corpuscles in millions.*
—·—·— *Reticulocytes per 100 red cells.*

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volatile oils from the point of view of determining their fungicidal action, and showed that thymol and carvacrol, its isomer, were the most efficacious. A culture of actinomycosis proved readily susceptible to an aqueous solution of thymol, but not to the other oils. He found that in one case of pulmonary actinomycosis, powdered thymol in capsules taken by mouth gave rise to great improvement, and he concluded that it was absorbed and circulated in sufficient concentration to have a fungicidal action. Local applications to sinuses of thymol in olive oil 10 per cent. solution have caused clinical improvement and recovery in the hands of Dr Myers, Dr Joyce and others, but in all the lesions surgical drainage had been performed or sinus formation was present. The dosage used was 1·5 gm. of powdered thymol in capsules given every two days out of three during the course of treatment, using up to 60 gm. in all and daily injection of the sinus with 10 per cent. thymol in olive oil.

Work has been done on the sulphonamides by Cutting and Gebhardt using cultures of a stock strain of *Actinomyces bovis* and cultures of *Actinomyces bovis* recovered from a discharging sinus in man. They came to the following conclusions: (1) aerobic and anaerobic cultures of the two strains were inhibited to some extent by sulphanilamide in a concentration of 10 mg. per cent.; (2) concentrations of 50-100 mg. per cent. checked growth more or less completely; (3) sulphathiazole and sulphadiazine were definitely more effective than sulphanilamide in similar concentrations. Eighty per cent. of my war group of cases received courses of sulphathiazole or sulphamezathine during their illness, but no dramatic improvement was noted. Dosage was in the region of 3-4 gm. a day for a ten-day course of treatment. It is interesting to note that these cases were on iodides and had all areas of softening drained, and as in-patients had daily controlled attention to their dressings, so that the factor of secondary infection had been largely limited. This state would probably account for the different views recorded by other workers who find a dramatic improvement in the first three weeks of treatment followed by a resumption of the chronic process even though 4 gm. of the drug is administered daily over a period of seven months. It would appear that the sulphonamides have no specific effect on *Actinomyces bovis* where the blood concentration of the drug is not higher than 9 mg. per cent., and that its main effect is the control of the secondary infection and will be most useful in the abdominal and thoracic form of actinomycosis where it is often difficult to provide adequate drainage, and prevent constant re-infection of the affected area from within.

Penicillin has been tried in a few cases where cultures of the isolated organism have proved sensitive to the drugs. From the point of view of sensitivity *Actinomyces bovis* reacts poorly to penicillin in comparison to the Oxford standard staphylococcus in the ratio of about one to three. I have used penicillin in a case of cervico-facial

actinomycosis in which a sinus had been present in the centre of a small area of induration for three months. The discharge was watery in nature and the lesion looked as if it would heal without further treatment, but the patient desired a rapid cure. Intramuscular injection of 100,000 units was given daily for ten days and produced no change in the clinical condition during treatment, nor in the following two weeks. Deep X-ray therapy was then administered so that the effects of penicillin could not be calculated over a longer period.

I had the good fortune to visit the E.M.S. Chest Unit at Hill End Hospital under the charge of Mr Roberts, where a patient suffering from advanced pulmonary actinomycosis was receiving continuous intramuscular penicillin therapy. A recent report in the *Lancet* has shown that the patient has made a dramatic recovery following two courses of penicillin therapy, the second course lasting twenty-eight days and the daily dosage being at the level of 200,000 units. The organism on culture proved to be atypical, and had the same sensitivity to penicillin as the Oxford standard staphylococcus. Another reported case of pulmonary actinomycosis developed a pyocyaneus pyæmia and died. In this case *in vitro* experiments showed actinomycotic growth of the organism to be inhibited in glucose broth by concentrations of 0·2 units per cubic centimetre but not by 0·1 unit per cubic centimetre. In the control test with the standard staphylococcus corresponding concentrations were 0·05 units per cubic centimetre and 0·025 unit per cubic centimetre. It would appear from reports of cases coming in that the sensitivity of the organism to penicillin has a wide variation according to the strain, and so a new method of therapy may also assist us to categorise in the future the virulence of the organism according to its strain, and thus explain the varying reactions of the patients to the disease. Not until we diagnose closed lesions of actinomycosis, isolate the organism by aspiration, prove it sensitive to penicillin on culture, and then treat with penicillin alone will we be able to assess the true value of penicillin.

Colebrook and other workers attempted to carry out active immunisation of the patient by the use of vaccine therapy about 1920. They were stimulated to try this line of therapy on the grounds that the disease was slowly progressive, and in many cases tending to self cure; that general health was unaffected for a long period, and growth of the organism in unaltered blood fluid does not take place as leucocytes are constantly ingesting it. Autogenous and polyvalent vaccines of *Actinomyces bovis* were used along with vaccines corresponding with the respective secondary infection, but in all the cases surgical drainage was associated with this form of therapy. Colebrook came to the conclusion in 1921 that vaccine therapy without adequate surgical drainage was of no value, but in drained cases he noted a rapid improvement under vaccine therapy where the disease process had set into a chronic state. The use of an autogenous or stock vaccine will depend on the answer to the question as to

whether or not there is a marked difference between the strains of *Actinomyces bovis* isolated from lesions in man. On the grounds that no marked difference between the strains has yet been proved, and the difficulties associated with making an autogenous vaccine from the material obtained from many of my cases in which sinus formation was present and secondary infection was often heavy, I have used a stock polyvalent vaccine. In cases suffering from the cervico-facial form of the disease I have used the vaccine in the dosage of 1-4 c.c. by injection on alternate days for a period of three weeks (1 c.c. containing 2·5 million fragments of the mycelium). I noticed no immediate clinical improvement, but surgical drainage and potassium iodide therapy were being used at the same time. No reaction was set up by the use of the vaccines.

Having reviewed the position of drug and vaccine therapy in relation to actinomycosis, I will now discuss the part to be played by the use of radium and deep X-ray therapy. I am indebted to my colleague, Dr Allchin, Honorary Radio-therapist to Westminster Hospital, for giving me his views on this aspect of treatment, so I now place them before you.

The principles on which the employment of radium and X-rays in the treatment of actinomycotic lesions are based vary considerably from those utilised in the treatment of neoplasm. In neoplastic disease the aim is to concentrate on a direct effect on the neoplastic cell, but in chronic inflammatory and actinomycotic lesions the indirect effects that the rays create are what we desire to use. These indirect effects are inhibition of cell activity, increased blood flow to the affected part, and an increase in the power of phagocytosis in the leucocytes surrounding the fungus. These changes are produced by small doses of radiation given twice or thrice weekly. The war series of cervico-facial actinomycosis all received deep X-ray therapy. The kilo-voltage was between 90-110, the filtration used was 2-3 mm. aluminium, and the focal skin distance was 23-25 cm. A dosage of 50-70 röntgens was given at one treatment. The majority of cases required about fourteen treatments with a total dosage in the neighbourhood of 1200 röntgens, but one case required thirty-two treatments over a period of six months with a total dosage of 2350 röntgens. The times of treatment were regulated according to the clinical response, the idea being to create clinical softening. When the inflammatory change was acute and the discharge profuse the treatment was withheld. Not only the time interval but also the dosage had to be varied, and on many occasions the treatment had to be stopped, for instead of causing localised softening the whole area would flare up in association with severe pain and pyrexia. I think that this state was dependent on the virulence of the secondary infection present, for surgical drainage always caused it to subside. The area to be treated should be large enough to cover all the indurated tissue and leave a good margin, for we know that the disease tends to spread peripherally and if we

can raise the resistance of the tissues we may hope to localise the condition.

In the abdominal cases smaller doses are given and the field is confined as far as possible to the site of the lesion. The reason for this change is mainly due to the fact that the lesion is constantly being reinfected with secondary organisms from the bowel, and irradiation stirs up acute inflammation in their presence. The dosage is in the neighbourhood of 50 röntgens twice a week for a period of four weeks, and the total dosage for one course should not exceed 600-800 röntgens. Other workers give intensive courses of treatment on the same lines as treatment for neoplasm, for they assert that nothing short of an adequate biological response is of value. Dosage used by them is in the region of 200-250 röntgens per day daily up to a total of 3000 röntgens. We find that any attempt to force a massive dose may produce such a reaction that treatment has to be stopped for an indefinite period, and as we do not consider that X-ray treatment is specific for cure of the condition, we prefer to use small dosage and vary it according to the clinical response.

Radium has been used in the past in the form of surface application, but has now been abandoned in favour of deep X-ray therapy. The great difficulty arises in giving an adequate dose to the lesion, and avoiding a skin reaction especially in the presence of sinus formation. In four cases of cervico-facial actinomycosis radium plaques were used containing an average of 60-80 mgms. of radium, 3-4 cms. distant from the skin, and a total dosage of 6000-9000 mgms. hours was given in a period of fourteen days. These cases healed up well, but administration of drugs and surgical drainage had formed part of the treatment. Radium plaques used in two abdominal cases contained about 100 mgms. of radium, but the application gave rise to no rapid improvement at the time, though one case healed and was well two years later. Deep X-ray therapy has now replaced the use of radium, as it is easier to apply and is more effective, but in cases with a deep-seated lesion that has undergone X-ray therapy for a long period with no response the radium bomb may be of value as it has more local penetrating power.

SURGERY.—It would appear from the evidence that has been gathered that the human body makes an attempt to extrude the causal organism of actinomycosis, and according to the tissue in which the organism lodges there is a large or small fibroblastic reaction in an attempt to localise the trouble. The presence of toxæmia is dependent on the destruction of vital cells or the presence of virulent secondary organisms causing liberation of toxins which circulate in the blood stream. We know that softening and sinus formation is Nature's method of extruding the organism and causing self cure, so that assistance by surgical drainage is the obvious line of treatment to promote cure.

In the past radical surgery was advised in the cervico-facial form

of the disease, but the case was usually seen at a late stage with the result that induration of the skin associated with multiple sinuses and heavy secondary infection was present, and response to antiseptics had been poor. I think that the results are now so good in this area of the body that radical excision of the affected tissue would only be justified in the rare case where there is a persistent solitary sinus leading to a small localised area of induration. In the cervico-facial form, surgery consists of supplying drainage at the correct time, and being prepared to do so on many occasions. Do not wait for the true sign of fluctuation before incising the area, for the amount of pus formed is often very small in comparison with the amount of necrotic tissue around. Softening of an indurated area is the sign to look for, and then a small central incision is made. I have found that the best plan is to use a spoon to remove the central débris, and then wrap gauze over the spoon and by a circular movement all the necrotic tissue that is ready for removal will come away and the tissue forming the barrier will not be traumatised. It is amazing to see the amount of débris that will come away, especially in the temporal region, leaving the skin grossly undermined. Drainage should then be kept free by inserting a small wick of ribbon gauze, and the whole cavity should be sprayed with sulphathiazole powder. A portion of *tulle gras* is applied over the area and then gauze and a bandage. Daily dressing and re-powdering of the wound should be carried out. I have not yet had the opportunity of using penicillin cream where the organism is sensitive, but it would seem to be a good alternative to the sulphonamides. When the areas of softening are incised the local condition rapidly subsides, and it has been suggested that this improvement is due to the fact that while the organism can propagate in necrotic débris, which has lost its antitryptic power, it is unable to do so in the lymph that flows into the area following surgical drainage. I do not think that more complicated measures are required, such as injection of the area with formalin solution, instillations of thymol or copper sulphate solutions, provided that chemotherapy and X-ray therapy are used in conjunction with surgery. When we come to the abdominal cases, I think that more radical surgery is required once a mass has formed and if sinus formation is present. I advance two reasons for this statement: one being that the constant secondary infection from the bowel is very difficult to control, with resultant poor response to low dosage X-ray therapy, and the other being the proximity of the liver and the high mortality once its cellular content is invaded. The fact that the spread tends to be retroperitoneal enables a large incision to be made over the mass and carried into the loin, and the content removed without disturbing the peritoneal cavity. Local sulphathiazole treatment can be carried out, and free drainage established so that the element of toxæmia from secondary infection is diminished and better access gained for irradiation. Radical surgery should be repeated if spread of the disease is not controlled.

The thoracic cases from the surgical point of view seem to fall into two groups. Those cases showing extensive lung involvement usually associated with a purulent effusion, and the other group in which the pulmonary signs are present, but the dominant feature is a swelling of the chest wall due to an underlying abscess or the presence of a sinus. The former group have a bad prognosis, as the cellular element of the lung is so extensively involved that it is difficult to establish free drainage. When the diagnosis is confirmed by aspiration the empyema should be drained, and the state of the underlying lung estimated. If the lung is obviously necrotic, as I saw in one case, the débris should be removed as far as possible to provide free drainage. In the latter group the abscess lying under the ribs is opened and free resection of the ribs, if they are involved, is carried out. The abscess cavity may lead into lung tissue or may be confined by adhesions, but it should be explored until a healthy barrier wall is reached. In the case of sinus formation on the chest wall, surgery will be required if the clinical state and X-ray films reveal spread of the underlying lesion, for it will mean that freer drainage is required. The latter group do better than the former, for by the time a primary localised abscess has formed on the surface of the thorax or a sinus developed, it means that the patient has some degree of resistance to the disease. Radical surgery is indicated, as spread is so difficult to control and secondary infection is usually heavy.

It will be seen that no matter where the disease attacks the body the surgical principles are the same, namely, assistance to Nature to remove the fungus and the débris formed, free drainage to diminish secondary infection, and avoidance of damage to the healthy tissue attempting to encapsulate the disease.

The conclusions we can now draw are as follows. The causal organism is anaerobic in its habits, and not to be confused with other aerobic actinomyces. The organism does not appear to be able to exist outside the body, so the theory of infection from sucking straw appears to fall by the wayside. The common condition of woody tongue of cattle has been differentiated from the disease of actinomycosis in cattle and man, and other diseases forming club-bearing granules have been classified. The nature of the growth of the organism has been investigated, and it would appear that different strains of the organism can be isolated which vary in sensitivity to drugs like penicillin, and may account for the different responses to treatment recorded by so many workers. The mode of entry of the organism has been discussed and it has been suggested that sepsis and trauma, especially in relation to carious teeth, may play a part in aiding penetration of mucous membrane, which appears to have a high resistance to this infection. Early and accurate diagnosis is essential if we are to cut down the mortality rate and gain good cosmetic results, but once the organism has entered a cellular tissue the prognosis is very poor. The value of various drugs has been assessed and a

place is found for the use of potassium iodide, the sulphonamides and penicillin. Treatment of the case is based on constant clinical observation of a changing state, and the choosing of the correct moment to apply the correct therapy in the form of drugs, irradiation or surgery. Adequate surgical drainage is the most important factor, for it assists Nature to extrude the offending organism and deals with the secondary infection so often present.

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NOTES

Royal College of Physicians of Edinburgh

A QUARTERLY Meeting was held on 1st May, the President, Dr A. Fergus Hewat, in the Chair. Dr James Ronald (Stirling) was introduced and took his seat as a Fellow of the College. Dr Cyril Hocken Tewsley, C.M.G. (Auckland, N.Z.), Dr Munir El Gazayerli (Alexandria), Dr Bryce Ramsay Nisbet (Kilmarnock), Dr Albert Arthur Huse (Birmingham) and Dr Ronald Haxton Girdwood (Edinburgh) were elected Fellows of the College.

Professor J. A. Nixon, C.M.G., of Bristol, was appointed Dr Alexander Black Lecturer for 1945.

Royal College of Surgeons of Edinburgh

AT a meeting of the Royal College of Surgeons of Edinburgh, held on 18th May, Professor R. W. Johnstone, President, in the Chair, the following who passed the requisite examinations were admitted Fellows: Frederick Edwin Douglas Hallon, M.R.C.S. ENG., L.R.C.P. LOND. 1937; Hassan Agha Hashemian, M.B., B.S. UNIV. LOND. 1942; Abdul Wasi Khan, M.B., B.S. UNIV. BOMBAY 1932, M.R.C.S. ENG., L.R.C.P. LOND. 1934; Walter Laurence, L.R.C.P. AND S. IRELAND, 1940; Maule Ramsay Liddell, M.B., CH.B. UNIV. EDIN. 1940; Charles Bryan Limerick, M.R.C.S. ENG., L.R.C.P. LOND. 1940; John William Peden, M.B., CH.B. UNIV. GLASG. 1919; Alfred Leonard Schofield, M.B., CH.B. UNIV. GLASG. 1933; Donald Moffat Sheppard, M.B., CH.B. UNIV. EDIN. 1938; Betty Vivian Slesser, M.B., CH.B. UNIV. EDIN. 1941; Ivor John Thomas, M.R.C.S. ENG., L.R.C.P. LOND. 1942; Maurice Elyis Winston, M.B., CH.B. UNIV. EDIN. 1938.

Henry Arthur Dalziel Ferns Bursary.—The Henry Arthur Dalziel Ferns Bursary was, after a competitive examination in organic chemistry in its application to medicine, awarded to Mr Morris Cyril Berenbaum.

NEW BOOKS

Health and Social Welfare. 1944-1945. Pp. 336. London: Todd Publishing Company. 1944. Price 21s. net.

Lord Horder, the advisory editor, in his introduction says that, in view of the great increase in the interest taken during recent years in health and welfare matters in this country, and of the large number of organisations and people directly interested in them, it has seemed desirable to prepare and publish a reference book dealing with these activities.

The greater part of the book consists of short articles on various subjects of current interest, summaries of recent committee reports and similar matters. One section gives the personnel of various ministries, boards and committees. There is also a series of short notices giving statements of the policy and work of a number of societies and bodies interested in the public welfare.

Tuberculosis of the Ear, Nose and Throat. By MERVIN C. MYERSON, M.D. Pp. ix+291, with 89 illustrations. Published by Charles C. Thomas, Springfield, Illinois, U.S.A. 1944. Price $5.50.

This book is essentially a record of personal experience based upon a series of over ten thousand cases of tuberculosis. It immediately commands respect as an authoritative statement of fact. More than half the book is occupied with the disease in the larnyx, and it is the most valuable portion as it contains almost exclusively results of personal observation. The other parts, however, contain an excellent account of present knowledge and practice. Each section is followed by a useful bibliography. The standard of publication is high, but the illustrations are not of the same class. This volume can be strongly recommended to those interested in this subject.

The Johns Hopkins Hospital and the Johns Hopkins Medical School—A Chronicle. By ALAN M. CHESNEY, M.D. Vol. I. Pp. xviii+318, with 37 illustrations. London: Humphrey Milford. Oxford University Press. 1943. Price 18s. 6d.

In these days when so much is being said about the reorganisation of established medical hospitals and schools, it is interesting to read the story of the origin and development of a school which within a period of fifty years has taken its place among the very best in America. This we can do in the fascinating chronicle of the Johns Hopkins University School of Medicine.

In the instructions he gave to his Trustees Mr Johns Hopkins desired that they establish a hospital to receive four hundred patients, which "shall in construction and arrangement compare favourably with any other institution of the like character in this country or in Europe." The hospital Mr Hopkins envisaged was what we would call a general voluntary hospital. It was to be for the behoof of "the indigent sick of this city (Baltimore) and its environs, without regard to sex, age, or color . . . without charge." The hospital was also to provide a training school for female nurses—at that time a novel proposal. Himself a member of the Society of Friends, Hopkins stipulated that while "the influence of religion should be felt in and impressed upon the whole management of the hospital . . . nevertheless, the administration of the charity shall be undisturbed by sectarian influences, discipline or control."

Although the terms of the gift made it clear that the Hospital and the Medical School were to be entirely separate corporations, it was the wish of the testator that the hospital should ultimately form part of the Medical School of the Johns Hopkins University, for the founding of which provision was also made in the will.

In implementing the wishes of the testator, the Trustees were "unhampered by traditions and free to work out their own salvation," and they set before themselves high ideals. As an integral part of a University, and with all the facilities afforded by close co-operation with a new hospital established on the most advanced lines, the school was to be more than a mere college for the training of medical practitioners. Its primary aim was to advance the knowledge of medicine on scientific lines by securing a clinical staff of the first order and providing them with every facility for research work, and by admitting as students only those who had by pre-medical study shown themselves capable of sharing in the work of investigation as well as in the practical application of science to the care of the sick. To mention only the names of Welch, Osler, Halsted and Kelly is sufficient to indicate the standard the Trustees set for their staff, and, to warrant that research facilities would be adequate, the students were required to have taken a chemical-biological course extending to about three years before entering the medical school; and the M.D. degree was not to be conferred on a student who had not studied Latin and could not read French and German with comparative ease.

The problem set to the Trustees of founding a medical school *de novo*, differed considerably from that which in the near future will confront our hospital authorities in reorganising long-established schools with all their traditions, conventions and

vested interests, so as to meet the claims of the many "plans," reports of committees and "papers" of different hues that are now in the air. The story of the early days of the Johns Hopkins Hospital and Medical School holds many lessons from which they may benefit, alike in the difficulties and setbacks that had to be overcome, and in the brilliant success that ultimately crowned the efforts of the founders.

Dr Chesney, whose thirty years' association with the school as student, instructor, associate-professor and Dean singularly qualify him for the work of historian, has accomplished the task with conspicuous success.

We look forward to the issue of the second volume, delayed by the war, which will continue the chronicle beyond the year 1893.

Exercises in Human Physiology. By Sir THOMAS LEWIS, C.B.E., F.R.S., M.D., D.SC., LL.D., F.R.C.P. Pp. xiv+103. London: Macmillan & Co. 1945. Price 3s. 6d. net.

Sir Thomas Lewis believes that the gap between pre-clinical and clinical studies can best be bridged by an extensive pre-clinical course in practical human physiology, and this book presents his proposals for such a course. Unfortunately, he has included only exercises based on his own researches, and so a restricted field of human physiology is covered. To the physiologist many of the exercises will seem trivial and unrelated to fundamentals; this is pardonable if the phenomena are of genuine clinical importance, but often this is not the case. As an introduction to Sir Thomas's own methods of investigation, developed by him into "clinical science," the book will prove valuable.

Backache and Sciatic Neuritis. By PHILIP LEWIN, M.D., F.A.C.S. Pp. 745, with 235 illustrations. London: Henry Kimpton. 1943. Price 50s. net.

In the preface Dr Lewin states that "This book gives the general practitioner the facts needed in the diagnosis and treatment of backache, and sciatica, and related conditions," and an impartial reader must agree that it goes far to establish this claim. The importance of a complete clinical and radiographic examination in all cases is emphasised, and the various forms of treatment by physiotherapy, manipulation and operation are fully described. While congenital, traumatic and pathological conditions in relation to the back are all considered, the chapters dealing with the intervertebral disc syndrome, and neuritis, neuropathy and sciatica are of particular interest. The industrial and medico-legal aspects of the problem are stressed throughout. Illustrations are clear and typographical errors few.

This book is a most comprehensive treatise and can be heartily recommended, not only to the general practitioner but to all those whose speciality includes conditions affecting the back.

Synopsis of Neuropsychiatry. By LOWELL S. SELLING, SC.M., M.D., PH.D., DR.P.H. Pp. 500. London: Henry Kimpton. 1944. Price 25s.

The author has made a bold attempt to present a condensed, almost tabulated, summary of neuropsychiatry. Quite a lot of neuro-anatomy, and some neuro-physiology, precede each section of clinical neurology. Subjects basic to clinical psychiatry, such as abnormal psychology, psycho-analysis and general ætiology are also discussed. Military and medico-legal aspects are mentioned—of almost every disease—which is often unnecessary. The book certainly does contain an enormous amount of information in abbreviated form. However, we think the author has attempted to compress too much; the undergraduate will find the text difficult to understand, while the postgraduate will find the presentation inadequate. No special attempt is made to integrate neurology and psychiatry, in spite of the title. The psychiatric section is the weaker of the two, and is so arranged that some repetition occurs.

There are a fair number of misprints, one or two involving dosages.

NEW EDITIONS

Clinical Electrocardiology. By D. SCHERF and L. J. BOYD, M.D., F.A.C.P. Second Edition. Pp. xiii+403, with 243 figures in the text. London: William Heinemann. 1945. Price 25s. net.

In the present edition the general arrangement and character of the book remain unchanged. No drastic alterations have been introduced, but some sections have been revised and some new records have been added. While the book deals principally with the conditions commonly encountered in practice, the authors have decided to include a description of such unusual phenomena as "super-normal phase" and "reciprocal rhythm," holding that a study of such things definitely adds to knowledge.

The book is an excellent exposition of this interesting subject.

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., D.SC., F.A.C.P. Fourth Edition. Pp. 1174, with 247 illustrations. London: Henry Kimpton. 1944. Price 50s. net.

Considerable new knowledge has become available in physiology during recent years, and the war has made increasing demands on the scientist. In preparing this new edition, the author has had to re-write approximately one-third of the text and has made many other alterations to include the most important recent advances. Of special interest are the sections dealing with shock, plasma depletion, dark adaptation, under-nutrition, acclimatisation, physical fitness and aviation physiology. These additions have necessitated a good deal of condensation and omission in other parts of the book. It still gives an excellent and well-balanced account of present-day knowledge of physiology. The book is one which should appeal to the clinician as well as to the student of medicine.

Elimination Diets and the Patient's Allergies. By A. H. ROWE, M.D. Second Edition. Pp. 256. London: Henry Kimpton. 1944. Price 17s. 6d. net.

The sub-title of this publication—a handbook of allergy—is a better description of the work than the title chosen, for the book covers a very wide field. Prominence, however, is given to the use of elimination diets in diagnosis and treatment. This line of approach to allergy was first proposed by the author in 1926, and the present scheme is an elaboration of the earlier diets.

Dr Rowe has made a very valuable contribution to the subject of allergy, and his book should be of the greatest interest to those working in this fascinating field.

The Practice of Medicine. By J. C. MEAKINS, M.D., LL.D., F.R.C.P.E. Fourth Edition. Pp. xviii+1444, with 517 illustrations, including 48 in colour. London: Henry Kimpton. 1944. Price 50s. net.

The author in planning this work has broken away from tradition, and his book has a character of its own. He places considerable emphasis on symptomatology, and where possible the cause of the symptoms and their significance are fully discussed. In contrast with the average text-book, this one is profusely illustrated with an excellent series of pictures which may often be more informative than a mere description in words.

The book is intended for practitioner and student, and to them we can confidently recommend it.

A Textbook of Histology. By E. V. COWDRY. Third Edition. Pp. 426+317 illustrations. London: Henry Kimpton. 1944. Price 35s. net.

Professor Cowdry has produced a "streamlined" third edition by omission of a certain amount of detail, but the book remains a presentation of structural physiology which goes far beyond the title. Written in an unusually attractive and readable manner, it gives an account of cell structure as it is concerned with vital function in the human body, and refers to current clinical and pathological literature wherever applicable.

The illustrations, both micro-photographs and diagrams, could scarcely be bettered; and the volume concludes with a valuable modern bibliography of over 500 references.

In a book so admirably turned out, it seems unnecessary to misspell the author's name on the outer cover.

Textbook of Physiology. By W. D. ZOETHOUT, PH.D., and W. W. TUTTLE, PH.D. Eighth Edition. Pp. 728, with 311 illustrations. London: Henry Kimpton. 1943. Price 25s. net.

In this edition the introductory chapter on protoplasm, and several other sections, have been rewritten; some new illustrations have been added and many of the original ones redrawn. There still remain a few old anatomical and histological illustrations which require attention. The book has been slightly reduced in size, but it remains, in our opinion, one of the best elementary texts.

BOOKS RECEIVED

BOYD, WILLIAM, M.D., LL.D., M.R.C.P., F.R.C.P., F.R.S.C. The Pathology of Internal Diseases . . . . . (*Henry Kimpton, London*) 50s. net.

BRAIN, W. RUSSELL, M.A., D.M., F.R.C.P., and E. B. STRAUSS, M.A., D.M., F.R.C.P. Recent Advances in Neurology and Neuropsychiatry. Fifth Edition . . . . . (*J. & A. Churchill, Ltd., London*) 18s.

BRAY, W. E., B.A., M.D. Synopsis of Clinical Laboratory Methods. Third Edition . . . . . (*Henry Kimpton, London*) 25s. net.

CHESTERMAN, JUDSON T., M.R.C.P., F.R.C.S., F.A.C.S. The Treatment of Acute Intestinal Obstruction . (*J. & A. Churchill Ltd., London*) 10s. 6d. net.

CROSSE, MARY V., M.D., D.P.H., M.M.S.A., D.R.C.O.G. The Premature Baby. (*J. & A. Churchill Ltd., London*) 10s. 6d. net.

ILLINGWORTH, CHARLES F. W., M.D., CH.M., F.R.C.S., and BRUCE M. DICK, M.B., F.R.C.S. A Text-Book of Surgical Pathology. Fifth Edition. (*J. & A. Churchill Ltd., London*) 42s. net.

LACE, MARY V. Massage and Medical Gymnastics. Third Edition. (*J. & A. Churchill Ltd., London*) 12s. 6d. net.

Edited by MONCRIEFF, ALAN, M.D., F.R.C.P. Psychology in General Practice. Published on behalf of *The Practitioner* by Eyre and Spottiswoode (Publishers) Ltd., London . . . . . 12s. 6d.

MORLEY, MURIEL E., B.SC., F.C.S.T. Cleft Palate and Speech. (*E. & S. Livingstone Ltd., Edinburgh*) 7s. 6d. net.

NAYLOR, ARTHUR, CH.M., M.B., M.SC., F.R.C.S. Fractures and Orthopædic Surgery for Nurses and Masseuses. (*E. & S. Livingstone Ltd., Edinburgh*) 16s. net.

PEARSON, WILFRED J., D.S.O., M.C., D.M., F.R.C.P., and ARTHUR G. WATKINS, B.SC., M.D., F.R.C.P. The Infant: A Handbook of Management. Third Edition . . . . . (*H. K. Lewis & Co. Ltd., London*) 4s. net.

ROWBOTHAM, G. F., B.SC., F.R.C.S. Acute Injuries of the Head. (*E. & S. Livingstone Ltd., Edinburgh*) 30s. net.

Edited by WAKELEY, CECIL P. G., C.B., F.R.C.S., F.R.S.E., F.A.C.S. A Synopsis of Surgery (Hey Groves). Twelfth Edition. (*John Wright & Sons Ltd., Bristol*) 25s. net.

WALSHE, F. M. R., O.B.E., M.D., D.SC., F.R.C.P., HON. D.SC. Diseases of the Nervous System. Fourth Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 15s. net.

WILLIAMSON, BRUCE, M.D., F.R.C.P. A Handbook on Diseases of Children. Fourth Edition . . . (*E. & S. Livingstone Ltd., Edinburgh*) 12s. 6d. net.

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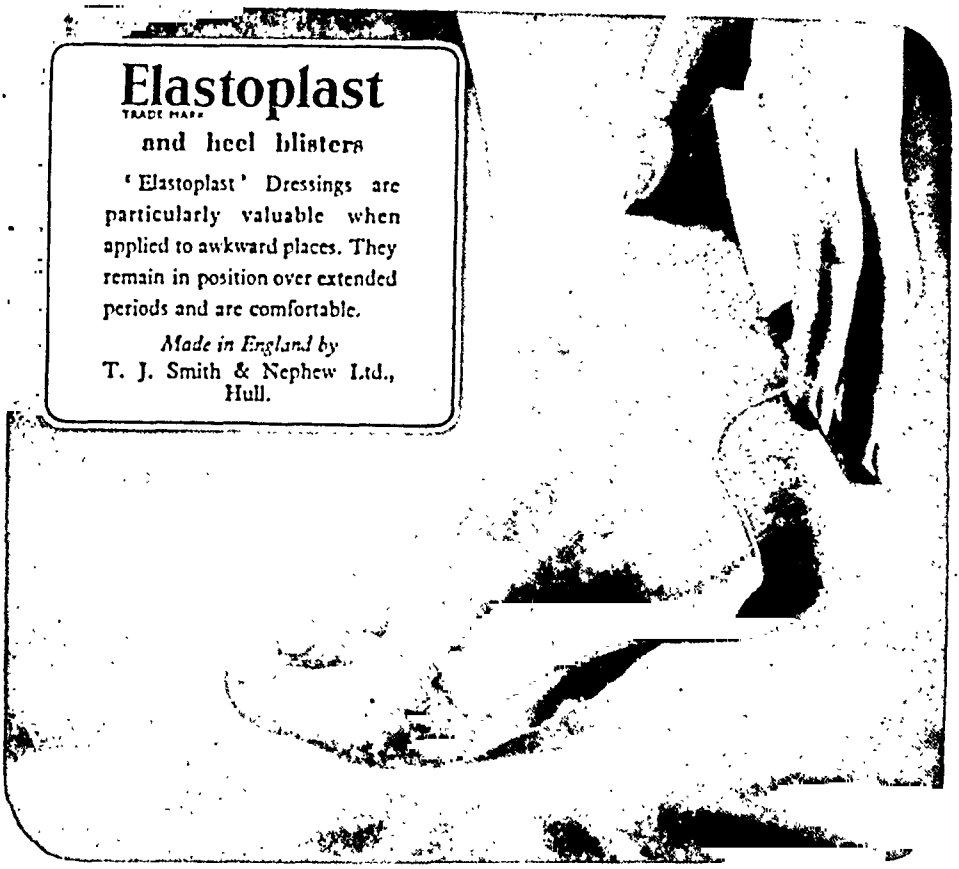

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THE TRANSITION FROM WAR SURGERY TO CIVIL SURGERY *

By WILLIAM ANDERSON, O.B.E., F.R.C.S.Ed.; formerly Brigadier, R.A.M.C., Consulting Surgeon to the Scottish Command

TRANSITION is always an interesting and exciting episode in our lives, and I need not remind you of the transitions which you have already experienced from nursery to school, from school to university, and soon, we hope, from university to practice. Hopeful anticipation tinged with doubts of our ability to fulfil our ambitions, and dread of the unknown and unpredictable, surround us as we approach such successive milestones in our lives. Each experience leaves an impression on our personalities, on our ways of thinking and on our relations with our fellows. I have been fortunate—or unfortunate—in that I have been allowed twice to experience transition from civil to military and from military to civil life, but the experiences have not been similar. In the first I was young, hopeful and enthusiastic; in the second, I am older and, to put it as kindly as possible, not quite so receptive. I hope to give you this afternoon flashes from a composite picture of these two experiences, and some of my reactions to them. It is, I would emphasise, a purely personal experience, and the opinions expressed are entirely my own. It may be helpful to you in explaining peculiarities in your colleagues returning from service, and so an interesting comparison for those of you who have had or will have a similar experience.

SOME EFFECTS OF WAR EXPERIENCE ON THE SURGEON

War is horrible, war is a filthy business. How often have we heard that quoted? I think it takes an experience as a doctor in a forward unit to drive home how horrible, how loathsome, how futile war really is. There the young surgeon sees, day in day out, week in week out, numbers of physically well-developed young men mutilated, suffering and dying. Those who are likely to recover are evacuated as quickly as possible, only the dangerously ill, the potentially dying, are left. In civil hospitals we also see death; but often the dying are

* A Guest Lecture in Surgery delivered at the University of Edinburgh on 7th December 1944.

old, or wasted by long-standing disease. To such as these, death is often a welcome release; but to the young soldier to whom living had been so good and so full of hope the sudden cutting off seems unfair and cruel, both to him and to us. Is it any wonder, then, that the young surgeon becomes shocked, numbed and ultimately cynical? The regimental medical officer sees one after another of his friends in the Mess become casualties. How he hates, for a few days, those sent up to replace them. Be kind, be tolerant with doctors fresh from Service when you meet them in their transitional stages to civil life. They have passed through a trying experience about which they will seldom speak. It is not "nice" to speak of such things; but if we are to know life, facts, however harrowing, should not be hidden. If everybody had served as a doctor in the last war there would have been no need for a League of Nations' Peace Vote in 1933.

In spite of the disappointments and hard work there are compensations: the gratitude and confidence of the patients, the urge to do more and more for such splendid men, the multiple opportunities for the display of initiative and resource, and the application of the best fundamental principles of our craft develop in responsive young surgeons qualities which in civil life will make him a leader and a teacher. Another and perhaps more important reward is that he has lived with, and got to know, men—not only doctors but combatants—not only men of his own age but seniors and juniors. This, I feel, gives him the chance—if he has sense to take it—of widening his views, of acquiring a better evaluation of the importance of the various problems of life, and especially of his own position in the universe; in short, of becoming a better citizen and therefore a better doctor. I like to impress this on the junior who after four or five years with field units returns with the feeling that he has forgotten all he ever knew. Any deficiency on the scientific or academic side is more than compensated by the experiences I have just detailed. I would emphasise that from the standpoint of operating, war surgery is bad for the man who has not had a proper and prolonged initial training; under stress and unfavourable surroundings his technique tends to become faulty.

Prognosis

We doctors forget the weight and importance which our patients attach to what we say—or at times what we do not say—and to our demeanour during interviews. As Consulting Surgeon, I saw the cases in which mistakes had been made, and so I have got an exaggerated idea of the problem. Still, we learn by our mistakes, and I hope that you will realise that such experiences are rather exceptional. I believe that "mishandling" is due to two main causes:—

(1) A very human but quite inexcusable desire to "show off." All humans wish to peer into the future—some even pay a soothsayer

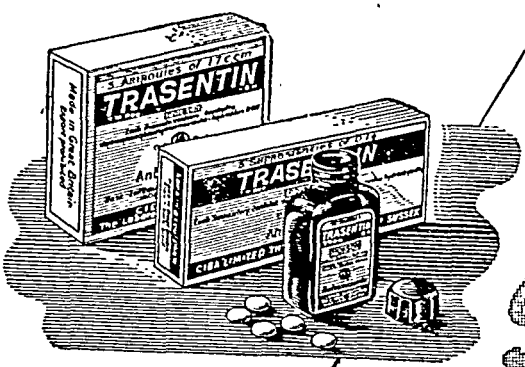
or palmist—and there is a delicious feeling of satisfaction in being *the* person who apparently by some superhuman power can foretell the future; it certainly does impress the patient. But if three or four specialists—and you have no idea how final a specialist opinion can be until you hear many patients say, "But the specialist said"—have each given their opinions, these may be sometimes entirely different, and sometimes almost the same, but said in such different ways that the impressions left in the patients' minds are so contradictory that the men become completely bewildered, naturally absorb the worst and forget the best, and ultimately become neurotic. I have listened to patients' versions of what they have been told, and almost became neurotic or apoplectic myself!

(2) Another cause of "mishandling" is our ignorance of the natural history of disease. In the text-books prognosis is given only scant discussion, and often in clinics is passed over in a single word—good or bad. We are not entirely to blame for this, as apparently similar cases may run very dissimilar courses. Your teachers in hospitals have too little idea of how long and in what discomfort patients suffering from mortal illnesses will have to live and die. They do not see such patients after they leave hospital. It is the general practitioner who can and should help us, and I trust that in the wonderful new world ahead the importance of a careful follow-up study of all types of cases will not be forgotten. Even when this is done, as I hope it will be, we must be careful not to apply generalities to the special case. For example, as a student I was told that the average life of a prostatic case put on catheter life was fifteen to eighteen months; that probably was and still is true, but I have known old gentlemen live comfortably for fifteen to twenty years who have never passed urine naturally, who never sterilised the catheter and who used saliva as a lubricant. It may be argued that we cannot assess from the exceptional, but the knowledge of exceptions should make our views and opinions less dogmatic. In giving a prognosis we must never forget that there is a vast difference between facts and reasonable deductions. A lump can, in fact, be felt, but its nature is, in the majority of cases, only a reasonable deduction. Please do not think that I decry deductions; they are the basis on which our treatment depends, and if we had to wait for incontrovertible facts we would get nowhere. All I ask is that where the man or woman's future happiness depends so much—so frighteningly much—on what we say, give the benefit of the doubt to a Christian understanding of the human being in your consulting room chair. You need not be dishonest, but there is no need to be "brutally honest" in order to sustain that somewhat precarious but zealously guarded attribute—your professional reputation. Often, very often, the honest opinion is "I do not know," and this can be paraphrased and tempered to the shorn lamb. Now perhaps you will allow me to illustrate some of the points which I have tried to make.

Varicose Veins.—A soldier aged forty-four was sent to see me for disposal. He had very marked varicose veins of both legs. His complaint was that the legs became tired and swollen. I asked him, "How long have you noticed these veins?" "A long time, sir." "How long is a long time?" I asked. "Well, sir, I was discharged for varicose veins during the last war." He had never had any treatment, had done nearly twenty-five years of hard manual work and had been in the Army a second time for three years. "Just can't keep up with the youngsters, sir." And that is not to be wondered at at forty-four years of age when one considers the strenuous course every fit man in the Army has to undergo. I doubt if many in this room—certainly not I—could stand up to these hard-trained youngsters. Another point: sometimes a pal and sometimes an over-enthusiastic medical officer tells a man that he has varicose veins. Up till that moment there have been no complaints, but soon the legs get tired, and sometimes there are even cramps. Then a more senior officer comes along, finds very slight varicosity and thinks the soldier is "skrimshanking." I do not think so. Knowing some aunt or mother who had a lot of trouble with varicose veins—ulcers, œdema—the soldier gets scared. He thinks that sooner or later he will be in the same plight; and then what will happen in civil life to himself, his wife and his children? As the veins were discovered in the Army, it is logical to conclude that Army life caused them, therefore the only hope is to get out of the Army or, at any rate, to have the veins treated. In the early stages we do not know which cases of varicose veins will progress to a disability and which will remain *in statu quo.* We do not know, although we may theorise about them, the factors which will influence the course of the disease. We still are doubtful how far we can influence the course of treatment, operative or conservative.

For these reasons it has been difficult to advise as to treatment. While watching a squad at physical training, a very large number of small dilated veins can be seen on the exposed calves, yet not one of these men has ever complained. I have been quite unable to assess the *subjective* as distinct from the *objective* symptoms of varicose veins. Much of the treatment is for psychological reasons. Injections alone will not give a permanent cure. Ligature at the saphenous opening as well as injection gives a more lasting cure, but we do not as yet know if it is permanent.

Feet.—The foot of the soldier is so important that the military surgeon's interest is necessarily directed to it. Even the so-called normal foot may break down under the strain of training and hard marching, while a disability which in civil life would have remained symptomless *may* under military conditions give rise to trouble. The proper fitting of socks and boots, the treatment of excessive sweating, and the maintenance of ordinary cleanliness are lessons which we as doctors could profitably preach in civil life. Most of the disabilities



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of the foot which in civil life gave satisfactory results following operative treatment are unsuitable for such treatment in the Army. Bitter experience has taught us that however beautiful the scar, however mobile the joint following operations for hallux valgus or hallux rigidus, the majority of soldiers on whom these operations are performed are never able to take their place in a front line unit. Flat feet, claw feet and deformed little toes gave the same ungratifying results, and it has been found to be better to downgrade the man and to treat him symptomatically. Hammer toe is the only condition which, as a rule, responded well to surgical treatment. Still, as is always the case in medicine and surgery, there are exceptions; and I have seen astonishing results from grossly mutilating operations, *e.g.* arthrodesis of the ankle. While giving every possible credit to the excellent work of the individual surgeon, I am sure that the man's will to get fit and to overcome disabilities has more to do with the result than the technique of the operation. You will thus see how difficult is the assessment of treatment even in a group whose environment, work and capabilities have been standardised. To repeat a well-known and at times hackneyed expression, "each case must be treated on its merits." I think, however, we have learned that function as distinct from deviation from the anatomically normal is the important criterion on which to base our opinions as to ability for work and as to the type of treatment (if any) which we advise.

The sharp unyielding upper edge of the toe-caps is a frequent cause of trouble in certain foot deformities, and the wearing of shoes or boots without caps frequently gives relief. The types of feet I have in mind have high arches and a tendency to claw foot with "sticking-up" toes. I presume the use of the toe-cap is to reinforce a vulnerable part of the shoe; but why bring them so far back? Do they really prolong the life of the upper? Any reform is up against Dame Fashion, and she is a difficult person to circumvent.

Backs.—In civil as well as in military surgery pain in the back presents a problem difficult of solution. In my experience it has not been more prevalent in the Army than in civil life. There is, however, one pathological condition to which I should like to draw attention. I refer to ankylosing spondylitis. As you know, this is a slowly progressive crippling disease with very indefinite signs in the early stages. I have seen several patients with painful backs, who, on the X-ray appearance of fusion of the sacro-iliac joints alone, have been diagnosed as ankylosing spondylitis; and, unfortunately, but quite honestly, the patients have been told this. After two or three years there has been no evidence of any progression of the disease, either clinically or radiologically. Movements of the spine are still good, and X-rays of the vertebræ show no abnormality. They are, however, by this time psychologically unstable. We have still a great deal to learn about the early signs and X-ray appearances of this disease, and also about its treatment.

Inguinal Hernia.—As was to be expected, this has been a common cause of disability in the Army, and treatment by operation has been the routine. One and only one point of real interest has emerged: the very high and unexpected rate of recurrence after operation. The absence of this knowledge is due to the very inadequate recording and "follow-up" systems for all types of diseases in our peace-time hospital organisation. Some modifications of the routine operative treatment have been suggested, but it is too early to assess their value.

Internal Derangement of the Knee.—On account of the training and duties of a soldier, traumatic disabilities of the joints, and particularly of the knee, are frequent in the Army, and a wonderful opportunity has been given for their study. Although I am a general surgeon, I have tried to learn something by watching those cases; and sometimes the spectator, even if only partially educated, sees most of the game. The surgical treatment of the torn cartilage is satisfactory, in that about 60 per cent. of the patients are fit to return to full duty. If we consider what full duty in the Army means in comparison to civil life, I think you will agree that this figure is good.

But in spite of all that has been written, and the wide experience of surgeons, it is sometimes very difficult to decide whether a lesion of a semilunar cartilage is present or not. While most patients give the classical history and show the accepted physical signs, a small minority do not. They are admitted and readmitted to hospital for recurring synovitis until ultimately a decision as to their disposal has to be taken. In the case of keen, intelligent and fully trained soldiers I have on several occasions advised an exploratory arthrotomy. In some—I have no note of the percentage—very obvious lesions have been found and a cure has resulted. In others no lesion sufficient to account for the symptoms has been demonstrated, and the patients have not improved or have been made worse. It is a very important decision, which must be made only after much thought. If the surgeon is more interested in his percentage recoveries than in the individual or in the man-power of the Army, he will refuse to operate on any but the straightforward case. Here let me say that contrary to what you might expect, and in spite of elaborate machinery, a "follow-up" in the Army is not easy. Men are posted to new units at home or overseas, special follow-up cards are lost or neglected, and the regimental medical officer gets tired of filling in forms which to him have no real interest. The knee is a vulnerable joint, and at the time of accident injury to structures other than the semilunar cartilages takes place. We attribute bad results to injury in the crucial or lateral ligaments, but that is not always the whole story. We have still a lot to learn about the knee joint.

"Iatrogenic" Disease.—My experience as an Army consultant has taught me how prevalent "doctor-made" disease is. It is a very chronic disabling disease, but does not lead to death. We all know the case of the man with a "weak" heart or the woman with

" colitis," who, by nursing the disability, leads a very long if somewhat useless existence; but there are other and more subtle forms of the disease. I have mentioned some already, such as varicose veins and painful backs. Often quite unconsciously and with the best of good intentions the physician has sown the seed. It may be by using technical terms of which the patient is quite ignorant; it may be an honest desire to be frank with the patient; it may be merely the unconscious expression on the face of the doctor during interrogation or examination; it may be that he said nothing when something was expected of him. Whatever the ætiology, the important lesson I have learned is how great is my responsibility, how great is my power for the happiness or misery of the patient's future life and how careful I hope to be in the future, especially during my clinics with students or graduates. May I hope that I have said enough to pass on the lesson to you?

The Soldier as an Individual

The duty of the Army is to beat the enemy. The duty of the Army doctor is to keep the soldier fit, and if he is sick or wounded to treat him so that he will return to fight as soon as possible. That may seem a hard-hearted statement, but it is nevertheless a grim fact. If we were to lose the war all our surgical and medical efforts would be valueless, and from the realistic point of view the individual—in wartime—would appear to be of no importance. This, however, is not the case, because the soldier is not a machine but a human being, and the military doctor is primarily a doctor. A good soldier must have a good morale. He must feel that if he is sick or if he is wounded every known method of treatment will be available and will be used. His relatives expect the same. It has been my duty and privilege during the last three years to help to see that he got it. That large slow-moving machine, the Royal Army Medical Corps, is not soulless. No soldier whom the doctors think will suffer from being kept in the Army will be retained; but on the other hand no soldier who is fit to serve will be allowed to pass on his duty to another man. Every case is carefully considered, first by the soldier's medical officer, then by a specialist, then by a Medical Board and finally by a special department in the War Office. In doubtful cases special reports and examinations are called for, often from a consultant. I cannot conceive of a fairer or more just method of dealing with the mass of varying problems which continually appear than that which has been evolved by the Army Medical Services through trial and error over many years of experience. From my small personal experience I know that where a doubt still exists the soldier will be given the benefit. I have no doubt that you have heard of some cases which you think are unjust and hard. Some of these have been referred for my opinion, and there is one thing which I have learned: never to give an opinion until I have accumulated all the facts about the case, and especially

in matters medical to *see the individual*. That I know is an old dictum, but it cannot be repeated too often. A file is no substitute for a consulting-room couch; a quiet talk will tell you more than a pile of correspondence.

Whatever the problem—the selection of a man for a special job, a clinical diagnosis, an inquiry into what appears to be a trifle—"see the bloke." A chance remark may give you the clue to the correct solution; his behaviour and bearing may lead you aright.

Army Life in Relation to a State Medical Service

It is with considerable trepidation that I approach this subject, but I feel that almost eight years' service in the Royal Army Medical Corps with over twenty years of private practice as a surgeon may entitle you to ask what I feel about it all. I cannot tell you my own conclusions (they are inconclusive), nor do I feel I would be justified in doing so. *You* are the people on whom will fall the responsibility of seeing that in the new era after the war the people of this country will be properly looked after from a medical point of view. The common people trust their doctors, and this makes the responsibility all the greater. I shall not live long enough to see any scheme fructify, but I have talked with many young doctors and I am confident that you, of the present generation, will see it successfully through. Being acutely interested in this my second transition from military to civil life at this time of suggested changes, I have discussed the problem of full-time salaried service *versus* part-time voluntary service combined with private practice with senior regular officers of the Royal Army Medical Corps and also with senior members of the Civil Service, men who have had a long experience of full-time salaried service. While many approve, others as strongly condemn service as they have experienced it. Arguments for freedom from the sordid financial aspect so incompatible with sickness and distress, security in old age, freedom from the bad influences and "dirty tricks" of competition by the first group are met by accusations of favouritism, toadying, playing for safety and "passing the buck" to the other fellow. I have received no help from this line of research! It would be wrong of you to allow the seniors to dominate the picture. I would advise you to seek, to weigh up, to criticise anything they may have to say, accepting as much or as little as to you the evidence warrants. It is in this spirit that I propose to discuss my thoughts on this absorbing subject.

Administration is a necessary part of a successful health service. In an unimportant and amateurish way I have been an administrator. Unfortunately there is often an undercurrent of antagonism between the administrator and the clinician, a feeling that the administrator is unknowledgable of clinical medicine, dogmatic and obstructive, and so unsympathetic towards the individual patient as to be almost

inhuman; a penpusher. On the other hand, the clinician is accused of being impracticable, unnecessarily obsessed with the importance of his own particular branch or speciality and, worst of all, unbusiness-like and stupidly sentimental. Both accusations are founded on fact; both are exaggerated. I feel that there should be no clean-cut distinction between administrative and clinical work. We have to deal with human beings, not motor-cars; and every action, every decision, *must* be human. An administrator must be first and foremost a good doctor, and a clinician a man of the world. Does it not ultimately come down to personality?—that elusive undefinable quality which we all know so well. I wish I could define it; I wish I could assess it accurately. I wish I knew how to nurture and develop it. I see my friend, Sir John Fraser, says that it springs from two roots—intelligence and the influence of environment. I am sure he is right, but only partially so; I would add heredity. However nebulous it may be, it *must* carry more weight than it has done in the past. Our leaders must be men or women of strong, honest, non-self-seeking characters, men whom we can respect and trust, who are sympathetic and understanding, constructive not destructive. It is therefore obvious, at any rate to me, that whatever type of health service is ultimately adopted, it must attract to the ranks of our profession such men as I have described. If it does not the service is bound to fail.

Red tape is the word we use when we have been frustrated! It includes discipline, refusal of, to us, legitimate requests, unaccountable delays, curtailment of freedom.

> "Freedom, without qualification, is an abstract noun which has a meaning which varies with each person's sense of values. Freedom is therefore one of those magic words beloved by politicians and propagandists. There have been numerous eloquent letters in the press about the imperilled freedom of the medical profession. However, in order to be properly moved by freedom it is best to listen to a brilliant after-dinner speaker; in these circumstances I have been so moved myself by mass hysteria as to be ready to sing with the best, 'Doctors never, never, never will be slaves.'
>
> "But in more sober moments when, in accordance with my creed, I have started 'to do my damnedest to pick holes in my own beliefs,' I have felt ashamed. No one can be fully free. Some men prefer freedom from the terrible bogy of bureaucracy, freedom from State medical dictators, and freedom to choose their own patients; therefore they chain themselves to the parish pump and endure the slavery of general practice. I preferred the freedom of the sea, freedom from financial cares, freedom from women, and the freedom to practise all branches of medical science; and therefore I chained myself to the quarter-deck and became a slave to their Lords Commissioners of the Admiralty." *

* Sir Sheldon Dudley, *Lancet*, 29th July 1944, p. 137.

All red tape is most irritating, and every one who has served in the Army has experienced it. Sometimes the obstruction is warranted —sometimes it is not. So long as we are a democracy and so long as we admit that all men are *not* equal in experience and knowledge, we shall have that sort of thing. An honest desire to understand the other fellow's problems leads to smooth working. There *must* be no narrow-minded, obstinately-sticking-to-the-letter-of-every-instruction attitude, but a liberal and *clinical* interpretation of instructions, taking into account *all* the circumstances of the case. Obedience to the spirit rather than to the letter of the law should be, and *is*, the aim on both sides. The plan of treatment is so much dependent on the opinion of the doctor in attendance that it is impossible and undesirable to lay down hard fixed rules. As a member of the Consultants Committee at the War Office, I have been responsible for some of the directives which have been issued to young surgeons. You will notice that they are called *Directives*, not Instructions; and I have found while going round that these Directives have been accepted, as a rule cordially, by my junior colleagues. Sometimes they will argue their merits or demerits, but that is a very healthy sign. Perhaps I might say, " Do not be afraid of Red Tape," but see that only the minimum amount is allowed. Once again I think you can see the great importance of personality. I have to add that my Service experience of Red Tape has been in the atmosphere of war. Perhaps in times of peace it is allowed to become somewhat redder!

I am sometimes asked, " From your experience do you think that a salaried or competitive service is the better?" This is an awkward question, because whatever reply I make I condemn my work either in the Army or in civil life. Let us look at it for a moment impersonally. There can, I think, be little doubt that for the ordinary man there must be both a stimulus and a goal which he can never attain; just as the donkey requires either a switch or a carrot, perhaps better both. It is therefore doubtful if complete security, presence of freedom, and absence of fear is for the good of the race or of a section of the race. Biologically such an utopian state of affairs means degeneration. Competition and survival of the fittest has been the law of nature throughout all time. That this somewhat heartless law may and does lead to abuse, and very frequently hardships to the individual, is only too true, and our civilisation demands that the " rights of the individual " should be guarded. In our planning we must be mindful of the dangers of transgressing the laws of Nature; if we go too far unforeseen consequences may make their appearance. What have been and still are the stimuli which have made our profession respected and trusted by the peoples of the world? What makes the doctor undertake the never-ending, exacting and worrying responsibilities which are demanded of him? Primarily it is to make a living—that he, his wife and children may be housed, clothed and educated according to accepted standards. I should like to think and to prove that such

mundane things do not obtrude so conspicuously into the picture, but it would be contrary to my observations on human life. I have noted in the Services that rank and promotion, increase of pay and allowances, are subjects for frequent discussion and causes of discontent and grousing. Money, not for itself but for what it brings—security, freedom, comfort and power—does play a large and important part in the lives of all human beings. It is sometimes forgotten that doctors are just ordinary mortals, and that their yardstick of a decent life is exactly the same as that of other men. But that money is not the only stimulus is proved by the fact that the possible monetary rewards in medicine are not so great as in some other walks of life. Another stimulus is the inward feeling of doing something which is satisfying; this has been so well put by the late Sir St Clair Thomson that I quote what he said when he was elected President of the Royal Society of Medicine in 1925. He held worldly ambition of so light and airy a quality that it was but a shadow of shadows, but he always nourished two ambitions. One was to till to the best of his ability the corner of the field of medicine in which he laboured, and the other was to accomplish this in such a way as to retain the esteem and regard and perhaps the affection of his fellow-workers. With what better ambitions could one start one's medical career? We wish to attract to the future medical services men and women of character and personality, of wide vision and of high ideals. In our planning this is the most important aspect to maintain, and, if necessary, to fight for. In my opinion the service given in the Army is of a high standard, but I have to add that stimuli are essential and that the emotional stimulus of war has played a part, the extent of which cannot be estimated. The absence of this stimulus must be allowed for in our post-war planning.

I have been privileged to see and to take part in the inner working of a vast and efficient organisation. I have met men and women whose responsibilities have been very great and whose decisions have important and far-reaching effects. I have met and been stimulated by enthusiastic clear-thinking juniors. In high stations and in low I have encountered the hard-working, uncomplaining, unselfish and non-vocal officer; on the other hand, I have met the fussy, noisy, self-seeking demonstrator; the conscientious, the hyperconscientious and the hypoconscientious. I have made friends, and those friendships I value and know that they will last. I have learned some of the many advantages of team work, but I have seen some of the shortcomings and pitfalls which must be avoided as far as possible. I realise, as never before, how great is the influence of the Head of such a team. His personality and his ideals in a peculiarly indefinable manner permeate the whole body, and on him to a very large measure depends success or otherwise of the scheme.

EMPLOYMENT AND HEALTH *

By T. FERGUSON, M.D., D.Sc., F.R.C.P.Ed., D.P.H.
Professor of Public Health, University of Glasgow

WAR has emphasised the importance of work in relation to health, an importance which cuts both ways, since, on the one hand, industrial efficiency is so much dependent on the health and happiness of workers, and, on the other, the whole circumstances of work profoundly influence the well-being of individuals. In the formulation of health policy there should be an effective link, closer than in the past, between industrial health services and the general machinery for the promotion of health.

I do not propose to speak in any detail to-day about the diseases of tradesmen ; that was well done by Ramazzini, the father of industrial medicine, nearly 250 years ago, and has been done by many other writers since. But I would plead for a wider recognition by doctors of the intimate relationship between work and health. There has been too much tendency to regard industrial medicine as a thing apart—a matter solely for the expert. Ramazzini wrote that to the Hippocratic formula for the investigation of disease he " presumed to add one interrogation more ; ' namely, what Trade is he of ? ' " and he went on to counsel, doubtless without malice, " when a Physician therefore is call'd to visit one of the poorer and meaner sort of People, I would advise him not to clap his hand to his Pulse so soon as he come into the Room, without enquiring into the circumstances of the Patient, nor to stand as 'twere, in a transient Posture, to prescribe where the Life of Man is concerned ; but to sit down by the Patient, let the Place be never so sorry, and carefully interrogate him upon such things as both the Precepts of our Art and the Offices of Piety require us to know." He was perhaps influenced by the teaching of Plato, who drew a sharp distinction in the Laws between the two types of doctors, one practising upon Freemen—he " carries his enquiries far back," the other upon slaves—waiting for them in the dispensaries, never talking to them individually or letting them talk about their individual complaints.

We have made some progress since the days of Plato and Ramazzini ; we now recognise that the reaction of an individual to his work is not peculiar to one stratum of society, and that unemployment may have results just as disastrous as work that is too exacting, alike for the individual and the community. Dr Yellowlees, in his 1939 Morison lectures, spoke of work—of congenial kind and reasonable amount——as " one of the most precious and stabilising gifts to jittery

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 3rd May 1945.

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creatures"; and Professor Mackintosh has written very wisely that "the miseries that disfigure the lives of great Societies are associated with enforced idleness, with drudgery, and with the fear that comes from insecurity." In 1937, 12 per cent. of young people between the ages of eighteen and twenty in Glasgow were unemployed, and in 1939 one-third of all persons in receipt of unemployment benefit in Scotland had been continuously unemployed for upwards of one year; it is scarcely possible to over-estimate the impact of such facts on national health and character. The connection between employment and the health of individual workers is clear enough. The background of employment has an even wider influence on communal health. The ugliness of the potteries, the drabness of the heavy steel areas of Lanarkshire, the squalor of our Scottish mining villages—these circumstances tend to choke the vitality and warp the outlook of the people. Mining is dangerous and unpleasant work, but the unfavourable mortality experience of miners is not wholly attributable to the factors of underground employment. The cheerless existence of the mining village has resulted in the mortality experience of miners' wives being relatively almost as unfavourable as that of miners. We do not fully appreciate the value to public health of the activities of the Miners' Welfare Commission, which aims not only at improving working conditions in the mines but at raising the whole standard of living and amenity in the coalfields.

In the past not nearly enough effort has been made to help young people to take up work suited to their aptitudes and capabilities; this becomes even more strikingly obvious in the presence of disability or threatened breakdown in health. In Scotland it was found in the Clyde Basin Experiment that some 6 per cent. of the young persons referred for consultation by their own doctors required change of employment if their health was not to be seriously undermined. An earlier experiment carried out just before the war to determine what could be done to minimise the increasing volume of long-continued incapacity for work among the insured population disclosed that of people who had been incapacitated by sickness for a period of three months, about 8 per cent. required change of employment if they were to have real hope of restoration to working capacity. Many of the men invalided from the Forces as no longer fit for further service are unable to return to their pre-war employment. Their need is not merely for guidance in the selection of suitable work, but for supervision of working environment and limitation of their hours of work and travelling time—in fact for a more physiological approach to the question of employment than has generally prevailed in the past, for it is probably fair to say that, despite the excellent work of the Industrial Health Research Board, the approach to industrial health has been too much that of the pathologist. It is true that specific occupational exposure may hold the key to diagnosis and treatment in some perplexing disorders of the chest, or of the blood or nervous

system, and that occasionally surgeons perform laparotomy for the relief of lead colic or heat cramps that are much more amenable to other lines of approach; but industrial toxicology is only a part, and, in the presence of effective supervision of working conditions, not a large part of the tale of industrial ill-health; that is really a tale of men and women bronchitic, rheumatic, cardiac, spent ere their time.

Osler knew well the risks of transition from the sheltered life of school to the maelstrom of industry. He thought it strange that we should surround children with increasing tenderness, only to toss them more or less at random into an atmosphere of dirt and fumes and chaos scarcely compatible with healthy living. Of recent years some effort has been made by the tightening of official machinery to prevent the worst abuses of children drifting into work for which they are unsuited, but such provision as there is operates only in a negative kind of way; of knowledgeable vocational guidance there is little The great majority of children are able to do most jobs likely to come to them in course of work, but there are some at both ends of the scale of physical and mental fitness who really do need assistance in choice of work. Nor is this kind of employment problem confined to the earlier end of working life. There has recently been a swing of the pendulum towards the view that the aim should be to secure for such old people as may wish it work that they can carry out without straining their own resources on the one hand, or unduly retarding the march of progress on the other; and if this school of thought carries the day, as it may well do, then there will obviously arise large questions affecting the organisation of industry. There is little to be said for keeping people alive unless they are to be left with some measure of the joy of living.

Working conditions still leave much to be desired. It is not too much to say that many Scottish workers labour under circumstances inconsistent with healthy living. Working conditions are fundamental; it is as fatuous to speak of industrial health in some moulding shops as it is to speak of public health in some slums. In the early years of this war we seemed to forget many of the lessons learned during the war of 1914-18 on the relation between output and hours of labour. Far too many people habitually worked shifts that were much too long, and even yet this matter has not received all the attention it deserves.

During the war there has been an enormous development of the employment of women in industry, and there can be no doubt that women have made a very great contribution to winning the war. That contribution has been made under conditions peculiarly difficult and in the midst of many conflicting claims. It is not surprising that there have been industrial casualties of many types among the ranks of these war workers. Too many of them are still working long shifts, even twelve-hour shifts, with added domestic responsibility and

time spent in travelling. Such conditions can lead only to disaster. There can be no doubt that many women, pressed into industry during the war, are having to carry loads far in excess of those that ought to be asked of them. The end of the war will doubtless see great changes in this matter; soon our politicians will be telling us that woman's place is the home. Meanwhile, even in war-time, a certain basic standard should be observed in the employment of women. Not very long ago an official memorandum thought it necessary to point out that a normal and uncomplicated pregnancy does not ordinarily involve incapacity for work, though during its latest stages, or in exceptional circumstances, a woman might become incapable. The way of the administrator is admittedly difficult, but in the light of the demands of much war work being done by women this kind of sophistry is strangely reminiscent of the technique of other days. The Industrial Health Research Board have pointed out that, however modern and well equipped its surgical and welfare arrangements, a factory is unhealthy if it fails to satisfy the deep-seated human desire to be treated as an individual, and not, as one woman described herself, "a number on an overall." It is disappointing that, despite some shining examples, so few factory managements appear to exercise any real thought for the happiness of their workers.

Since 1940 welfare facilities in factories have been developed and new attempts to promote the health of workers have taken two chief lines: one, the provision of canteen facilities—a very great step forward; and the other the appointment of medical officers and nurses to work in many factories engaged in war work. The usefulness of these doctors working as industrial medical officers would be enhanced if the basis of their appointment was satisfactory, which it is not; for a man employed and paid by an industrial organisation cannot always hope to enjoy that freedom of action which is essential if he is to achieve the best results. There must often arise a sense of frustration. Further, the relationship must be apt to create in the minds of workers a suspicion that the medical officer is primarily an instrument of efficiency engineering; nor does it help to foster the very necessary close co-operation between family doctor and industrial medical officer.

Industrial efficiency, in the sense in which we as doctors are chiefly concerned, represents the sum of many factors—the whole factory environment, hours of work, canteen facilities, health care, work related to aptitude, congenial relationship with foremen and fellow-workers, and the host of extra-factory relationships which influence very directly human happiness and the quality of human work. It is not surprising that the family doctor and the specialist are often in doubt about the effect of employment on a patient's health and about the patient's ability to continue without hurt to himself at the work on which he is engaged. One major difficulty is that of assessing the physical demands of the job, for nowadays doctors in busy industrial

practice must find it difficult to be familiar with the employment of their patients, though it would help them enormously in their work if they had some knowledge of this kind; another is the difficulty of assessing how far the origins of psychological difficulties have their roots in employment, and whether in the employment as such or in some conflict with factory personnel. These difficulties are aggravated by the element of compulsion involved in the direction of manpower.

There are many people whose state of health is such that they can almost at any time declare themselves unfit for work, and present the doctor with an extremely difficult task to disprove their assertion. They can be "fit" or "unfit" very much at their own choosing, and that choosing is apt to be determined by how their work and working environment appeals to them, as well as by the extent of their financial dependence on the difference between wages and sickness benefit. Sometimes they make spectacular improvement when such circumstances change. These people are always liable to be a source of friction between doctors in practice and the administrative machinery, which is apt to have a preference for medicine by mathematics. Some find their way into work for which they are quite unsuited; for some the only prospect of continuing working capacity lies in change of employment. The determination of capacity for work has troubled the administrator ever since an Act of 1579 sought to punish strong and idle beggars, but to relieve the poor and impotent. Sir George Nicholls, an outstanding civil servant of his time, wrote in 1856 that the question of ability for work must in many instances be extremely difficult to assess: "A man may be able to do some things, and not able to do others—he may be able one day or one week, and be unable in the next—he may be able in the morning, but if left without sustenance during the day he may be disabled in the evening." Sir George recognised that uncertainty about fitness for work "will often occur, even to the most practised observer, and this independently of the nicer question as to the precise extent or degree of disability." Before the war the Regional Medical Officers, on whose shoulders hung the mantle of Solomon in these matters, used to classify their clients as fit for work, unfit for work, or fit for alternative employment. The general principle was that a man was marked fit for alternative employment when it seemed probable that he was not likely to be able to return to his old work, yet was not wholly unfit for work of any sort. Here is what the official Memorandum, issued to general practitioners, says on the subject (307/IC Scotland 1940):—

> ". . . Though the fact that an insured person is unable to follow his ordinary occupation is not in itself sufficient to justify his being regarded as incapable of work, yet he would properly be so regarded if, as will ordinarily be the case, it appears probable that he will soon be able to resume his former work, and that it would therefore be unreasonable to expect him to undertake any

other form of work in the meantime. . . . At varying stages in the course of different diseases, or after the occurrence of particular injuries, it will become clear that there is no reasonable prospect of the patient again becoming able to resume his ordinary occupation. . . . When this condition of permanent incapacity to resume the ordinary occupation has supervened, a different criterion from that of fitness for that occupation must, it has been held, be applied, and the patient should not be certified as "unfit for work" unless, in the practitioner's opinion, he is physically unable to perform any other suitable kind of remunerative work, whether at once or after a short course of training."

This position obviously lent itself to heart-burnings, the more so since before the war there was no very effective mechanism for helping the partially disabled man to obtain alternative employment. The war has changed the position very materially, partly by increasing the demand for labour, even the so-called "sub-standard" labour, and partly because of the introduction of new machinery for the resettlement of the disabled in suitable work.

Colonel Cunningham and Major Duthie have already spoken in this series about certain aspects of rehabilitation. Ever since the awakening of interest in this subject in the years immediately before the war, authorities have insisted that it should be regarded as a continuous process, extending from the onset of disability right up to the point of successful return to suitable work. It is generally agreed that, taking the working population of the country as a whole, there has not in the past been continuous effective supervision extending to the point of return to work. Still less have there been for any considerable proportion of the working population facilities for modifying industrial conditions to help to counteract these departures from optimum health that are so apt to prejudice the well-being and efficiency of workers. Some progressive employers have for long tried to safeguard the health of their employees along these lines; generally speaking these are firms that have studied and maintained a highly satisfactory standard of working environment. For the most part they have been engaged in light industries where health problems do not always present the same difficulties as in heavier trades, though it had already been demonstrated before the war that, even where work was heavy and working conditions exacting, a good deal could be done by sympathetic management and efficient treatment to preserve health and reduce incapacity. These localised efforts only served to emphasise their general dearth throughout the country. In the development of a new service it would be wrong to regard rehabilitation as a convenient cloak for faulty medical service on the one hand, or faulty working conditions on the other.

It is well known that the existing mechanism of Workmen's Compensation often interferes with the full fruits of efforts to restore

working capacity. There have been many instances of men discharged from Fitness Centres as "fit for work" but unwilling to return to work pending the settlement of compensation claims; the men inevitably deteriorate during the weeks while settlement of claims is pending. Then there is the vexed question of light work. Light work within the industry in which a disabled man was employed prior to his incapacity may be a legitimate, and indeed the most satisfactory, method of restoring him to full fitness for work, but safeguards are necessary to prevent abuse of light work and to see that no man is allowed to drift along indefinitely in light work if he is in fact able to do something better. Light work should be approached as a graduated process of restoration to full working capacity, and should be intelligently supervised.

Fortunately most people are able to return to their old work after an illness, and, in general, return to old work is the ideal—provided such work is not likely to aggravate disability, for there is something of the joy of craftsmanship that invests return to a man's trade with especial satisfaction. But there are some cases in which change of work is necessary, and it is important to recognise that the question of resettlement of disabled men in suitable work is one that has a large medical component, and that the profession must take its place in this new field of service, for it would be disastrous to allow the medical interest in this matter to go by default. It cannot be too strongly emphasised that a layman armed with a medical dictionary, however good, is no substitute for skilled medical assessment of the individual case, and may even be a serious menace in dealing with the problems of disabled men, as in many other spheres. Laymen are usually ready enough to recognise the employment limitations of such gross surgical conditions as amputations, but, even with the best intention, much less appreciative of the difficulties inherent in many medical disabilities, such as cardiac disease and epilepsy, though these conditions usually present far greater employment difficulties than the others. When the demand is for fitters there is a big temptation to allocate to fitting a disabled man whose industrial background lies that way, even though fitting is not really compatible with his disability; and that is one certain way to produce industrial casualties.

Efforts to help disabled men can only succeed along the lines of individual approach and appraisal. Any attempt to mass-produce courses of action for groups of disabilities must inevitably fail, for within disability groups there are many variations in the needs of individual men. The broad lines of approach to the resettlement of disabled men have been defined: What job can he do productively and happily? Can he do it without danger to himself or the community? Does he require continuing medical supervision? These considerations imply a much closer association than usually exists between the doctor and the industry of the area in which he works as general practitioner or as a member of a hospital staff.

American experience has shown that nearly every disabled person is capable of doing some useful work, unless he is ill in the common meaning of the term; but if all these disabled people are in fact to be re-settled usefully into industry there must inevitably be a reorientation of the outlook of industry towards the disabled, and, in some cases, of the outlook of the disabled towards industry. While in advising disabled men on employment it is necessary to keep ever in mind the importance of ability rather than disability, it must also be remembered that many men in their keenness seek to undertake work beyond their physical compass. It is a serious thing for a man to give up the employment in which he is skilled, for such a course may be fraught with psychological and economic implications. My experience has been that even where change of work is absolutely necessary, some disabled men hesitate to take the step. I have often seen coal-miners or quarry-men with silicosis and considerable shortness of breath who were reluctant to give up work which they knew well had already undermined their health and would certainly hasten their end. This reluctance springs sometimes from a real fondness for their work, sometimes from financial considerations, sometimes from unwillingness to leave their home village, often barren of alternative employment, sometimes simply from the difficulty of finding another house. It is not uncommon to find disabled men working long shifts at distances from their homes, which may involve as much as three hours' travelling time daily spent in awkward journeys, and this additional strain often precipitates breakdown. Even where the need for change of employment has been accepted and a man trained for some work consistent with his disability (*e.g.* instrument making), it sometimes happens that, after training, he finds that his new dexterity enables him to do some other job (*e.g.* maintenance fitting), and he may take the first opportunity of switching over to this more highly paid work, even if its physical demands are too great for his strength.

The attitude of employers to the disabled varies widely and often influences materially a disabled man's prospect of success. Some are more zealous than others in their attempt to find suitable work for a disabled employee. It is sometimes possible to develop as a positive asset a man's knowledge of his trade even if he is unable to continue as a tradesman at it; given some commercial training, he may become a first-class salesman with the priceless advantage of practical experience of the materials he seeks to sell. Even more important than the attitude of the employer himself is the attitude of his foreman. A foreman's life is not a happy one, for he is apt to be crushed between the upper millstone and the lower—between the demands of production on the one hand and those of labour on the other. It is perhaps asking a good deal to expect him to smooth the path of the disabled workman, sometimes at the expense of these minor adjustments that may help the disabled so much but do inevitably cause a little temporary dislocation in the even tenor of manufacture.

The attitude of the workmates of the disabled man is another important factor. I have repeatedly come across cases where a disabled man was enabled to carry on by the sympathetic help and kindly tolerance of his mates. Severely disabled men, particularly, are sometimes able to do surprisingly well if they can go back not only to familiar jobs but to work beside the workmates with whom they used to serve. For the disabled man there is nearly always at first a warm welcome, but it is perhaps only natural that sometimes with the flight of time jealousies and grumbles arise, and may well come to be a serious factor in successful resettlement.

The passing of the Disabled Persons (Employment) Act last year has opened an entirely new chapter in the care of the disabled, contemplating as it does their registration and re-settlement with a statutory obligation on industry to employ a quota of disabled persons. The intentions of the Act are above reproach, and it has been hailed as a charter for the disabled; but its administration will bristle with difficulties—difficulty over registration, over the regimentation of the disabled that the Act may very likely involve, over quotas in particular industries, over the assignation of men with particular disabilities or idiosyncracies to particular factories, over the employment and remuneration of "dilutees" and over many similar questions. The Act makes provision for advisory machinery, national and local, with some medical representation, but it is difficult to avoid the impression that in matters of day-to-day administration the officers of the Ministry of Labour will need wisdom and breadth of outlook, together with a measure of elasticity not always inherent in Government service. It is a pity, when far-reaching legislation of this kind was under contemplation, that opportunity was not taken to profit from the experience of Denmark in attempting to discover "invalidity" or potential "invalidity" at the earliest possible moment, for the earlier the approach to re-settlement the better is the prospect of success. In Denmark there is a system of notification by doctors and the heads of schools and hospitals of all potential "invalids" between the ages of seven and thirty. In 1938, from a total population of about four million inhabitants, there were 1735 notifications; these disabled persons received thorough medical and surgical overhaul, and steps were taken to help them to shape their careers. Of those who received vocational training, about one-third were trained in scholastic subjects (teaching, commercial work, milk recording, etc.), and two-thirds in various artisan trades (shoemaker, painter, joiner, seamstress, hairdresser, etc.). The Danish system seemed to work well. Disabled persons handled under it certainly were enabled to increase their earning power, and, for the most part, were able to hold the employment for which they were trained.

Already in Scotland we have been able to review the experience of some thousands of disabled persons during the war. Among one group of over 1600, mostly ex-Service men, but including over 300

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civilians, about 18 per cent. were found to be unemployed six months after seeking help to find suitable employment. Some disability groups returned better results than others. Among those who did well were men whose disability was psychoneurotic in nature, and men suffering from peptic ulcer. At the other end of the scale were men suffering from cardiac and organic nervous disease, and, least favourable of all, from tuberculosis. Of men who were accepted for vocational training, nearly 20 per cent. failed to complete their course of training for one reason or another, and of those who failed about half were forced to give up on medical grounds. Generally speaking, the longer disability has been present, the less satisfactory the prognosis; younger men do best in relation to training for new employment. It is essential to keep touch with a disabled man for at least six months after his return to work to be sure that he is in fact settled in work he can perform. Failure to keep this continuing contact is the cause of considerable failure.

Disabled men encounter many difficulties. Some find their work too heavy; some that long travelling to work on top of a heavy working shift is too much for them; some have difficulty in obtaining tools; some have difficulty in obtaining suitable clothing; many have financial troubles, the wages they are able to earn being too small for their increasing responsibilities. Many chafe at what they think are irksome pensions delays. Many have difficulty in getting a suitable house; a disabled man may have almost as much difficulty in making his way up and down the stairs of a high tenement house as in doing his day's work. Added to their disability is the difficulty—often formidable—of settling down, sometimes aggravated by disappointment and disillusionment. The extent to which the medical, social and employment aspects of the difficulties of these men are interwoven is indeed remarkable. They cannot be dissociated, and any approach that regards the man simply as an employment problem must inevitably fail.

It is my plea to-day that doctors should take greater interest in the work and working background of their patients. These are major health issues from which medicine cannot afford to stand aloof, partly because of their direct repercussions on medical practice, and partly because medicine can bring to their solution a contribution and a breadth of outlook of its own; such things are of the very essence of Social Medicine.

THE BASIC SCIENCES IN SURGERY*

By J. Z. YOUNG, M.A.

From the Department of Zoology and Comparative Anatomy, Oxford

THE development of a technique such as that of surgery occurs not only through experimentation by the practitioners themselves but also by the importation of the results of other inquiries not immediately aimed at the same mark. It is therefore of the greatest importance that professional organisation shall provide opportunity for the continual mixing of diverse currents of ideas. Anyone immediately occupied with a practical object is bound to be more or less limited in his view of methods and possibilities, if only by the urgent necessity to do something. This applies particularly in medicine, where the ethical situation severely limits the possibilities of experiment. Considerable advances must therefore come about largely through more or less indirect approaches. The question of how best to mix the currents of inquiry is evidently a very difficult one. Ideally, various disciplines should be included in the mind and practice of each person engaged in the profession. The surgeon or physician who is also learned in the basis sciences (or, indeed, in the arts) can play a tremendous part in the development of his subject. But as methods have become more elaborate it has become impossible for anyone to achieve the wide range that he would desire. It is still important that during his education every medical man should acquire as great a familiarity as possible with the aims, methods and results of the basic sciences, but this alone will not suffice to give medicine that connection with other subjects which is necessary for its development.

It may be interesting therefore to give you some account of the progress over a number of years of an experiment in co-operation between biologists and surgeons, in the attempt to produce improvement in the methods of the surgery of peripheral nerves. As a result of the stimulus of war, the problem of co-operation was approached both more suddenly and more consciously than is perhaps usual, and it is therefore possible to give a reasonably satisfactory and accurate historical account of the interplay of ideas between the hospital and the laboratory.

Throughout there may be said to have been two distinct currents of inquiry: (1) into the basic processes of nervous regeneration, and (2) into technical matters arising in the course of surgical practice. Having already some acquaintance with the first, during the autumn of 1939 I began to make myself familiar also with the literature of

* A Guest Lecture in Surgery delivered at the University of Edinburgh on 30th November 1944.

the more practical problems. Nerve injuries are not very common in peace-time, but since Weir Mitchell's classical investigations during the American Civil War, each conflict has stimulated an outburst of inquiry, in an attempt to find methods of dealing with injuries both more numerous than, and different from, those which have to be handled in civil practice.

The survey of the literature proved most instructive to the biologist, the most striking fact being that though many problems were raised, few or none were ever solved. In spite of sustained attempts at analysis of results, such as those of Platt, Bristow and Stopford in this country, Stookey in America and Foerster in Germany, hardly any of the more interesting questions were satisfactorily decided. Indeed, because of the variety of the cases and of their treatment, questions could hardly ever be asked in a form in which they could be categorically answered. Many surgical papers consisted in the description of the results of series of cases often leading to a discussion of their bearing on various problems, but allowing only the expression of the writers' general impression as to the answers. Now the basic scientist attempts so to frame his questions that when he has made his observations he can express the results as propositions which are true. That is to say, they are easily understandable and can be verified by anybody. This sounds so elementary as to be hardly worth stating, but in fact in all sciences the practice is only an approximation to this idea. In the physical sciences the approximation is quite close, in biology we have often to be content with dusty answers, and in medicine we are lucky if we can even ask clear questions at all.

In fact, one of the most important contributions which the basic scientist can give to medicine is to urge and demand that the clinician, and especially the clinical research worker, shall not be content with vague opinion but shall employ respectable criteria of logic and analysis in his work; in particular one notices in much surgical inquiry the absence of quantitative treatment. The statement that one procedure is more satisfactory than another is a quantitative statement, and the scientist is entitled to ask for the figures on which the claim is based. Often there are none, and the clinician will sometimes strongly maintain that it is impossible and even undesirable to provide them, since "figures can be made to prove anything" or "it all depends whose figures they are." Now the scientist has learned that his work consists largely in breaking through this attitude, while recognising at the same time that it has a genuine point. A rule which a biologist, at any rate, finds useful is to suspect both those who lay down that results must be quantitative, and those who deny that they can be; but particularly to suspect the latter.

Therefore, with considerable hesitancy, I ventured in the autumn of 1939 to frame a series of questions to which it seemed that clear answers were desirable as a basis for advance in peripheral nerve surgery. Some of these were questions which could be answered

only by collection of suitable clinical data; others could be approached experimentally. Before I proceed to discuss some of these questions and their answers, it will be necessary to explain how the organisation for dealing with them grew up.

We began experiments immediately, using rabbits, and by the summer of 1940 had begun to get some preliminary answers, though we hardly realised at the time how incomplete they were. Meanwhile we had been able, largely through Professor, now Brigadier, H. Cairns, to learn something of the problems as they appear to the practising surgeon. In November 1940 the Medical Research Council initiated its Peripheral Nerve Injuries Sub-Committee (later Nerve Injuries Committee), under the chairmanship of Dr, now Brigadier, George Riddoch. This committee has succeeded not only by initiating or supporting actual individual research investigations, but even more by the opportunities it has provided for exchange of ideas, and by producing that loose integration which is for some purposes the most efficient kind of organisation. It has afforded just the right occasions for the mixing of currents of ideas from different fields.

Meanwhile, on the administrative side, a policy had been agreed upon whereby cases of peripheral nerve injury were segregated to one of a small number of specialist centres. This policy may have certain inconveniences, but there can be no doubt that it provides both the best treatment for the patient and the best opportunity for the development of the subject. If I should suffer a nerve injury, I should certainly prefer that it be treated at such a special centre rather than by a surgeon, however good, who had only a limited experience of such cases.

In Oxford we were fortunate indeed in the advent in the summer of 1940 of Professor H. J. Seddon as Professor of Orthopædic Surgery. The Wingfield-Morris Hospital became one of the centres to which nerve injury cases were segregated, and we had constant opportunity to watch operations and to discuss cases. In return we provided experimental facilities in the Department of Zoology for Professor Seddon and others on his staff, especially the late Bremner Highet, whose loss while on his way to treat nerve injuries overseas was a tragedy for us all and for the subject. We also undertook the pathological work on the pieces removed at operation, a very valuable corrective to the pretty ideas about wounds which one is apt to get from simple animal experiments.

This gives only a rough idea of the main channels which were available for contact with surgeons and neurologists; it would not be possible to enumerate the many rivulets contributed by friendly meetings and discussions with individuals all over the country. After this long preliminary we must return to the history of the original ideas and questions posed. How have they developed, and how many have been answered? I shall try to explain them to you accurately and historically; this lecture is indeed, as I hope you may by now have

recognised, something of an experiment in what I hope I may be forgiven for calling exegesis.

Our first list of questions is before me, and it begins with: "1 the *vis a tergo* or tendency to grow out. i. 1 What is the effect of repeated cutting? Do axons grow out as well after a second as after a first section? Can this process be repeated indefinitely? If so, what is the optimum interval between operations?" And there follows a note, "These are very important questions in deciding whether, other things being equal, to adopt radical or conservative methods after section of a nerve has been proved. The clinical literature on this question is full of disagreements since it involves the whole problem of conservative *versus* radical treatment of presumed severed nerves. Thus Platt (1921) suggests leaving an initial waiting period of six months before attempting suture, and Foerster (1934) from a long series of cases concluded that 45 per cent. of severed nerves heal 'spontaneously.' On the other hand, several surgeons (Lewis, 1920) have commented on the greatly increased chance of recovery after early suture, and have claimed that suture at periods longer than one year after injury is seldom successful. As Babcock (1919) points out, there is no logic in concluding that stumps cut with a bullet are more favourably placed for healing than they would be after suture. It is fallacious to refer to the conservative method of treatment as the more 'natural.' Further, even if, as Foerster and others have shown, numbers of severed nerves show recovery without suture, it does not follow that this recovery is the best that could be obtained. Throughout the literature on the subject, both clinical and experimental, there is constantly apparent the lack of sets of standards by which degrees of regeneration can be compared. One of the most urgent needs is for the establishment of these, and in general for the long-term following up of cases."

Here is expressed the essence of the problem which is perhaps most central in dealing with nerve injuries, namely, when to operate; and I shall deal now with the development of ideas on this question without waiting for the other items on my list of December 1939. Evidently the question can be answered in one of two general ways, either (as suggested) by adopting sufficiently rigorous standards to enable quantitative comparison of degrees of recovery achieved in man after various procedures, or by measuring the rate of regeneration in experimental animals under various conditions. Curiously enough, the question of the rate of regeneration is not mentioned as a specific problem in my list, although in December 1939 we were already working on it. Perhaps it was so evidently implicit in all the questions that it did not occur to me to put it down. Or was it unconscious caution? For the rate of nervous regeneration is like the Cat in *Wonderland*. As one looks at it, it fades away and one finds that what one has discovered is that there is nothing to be found. In our earliest experiments we severed and joined rabbits' nerves and then at

various intervals lightly anæsthetised the animals and by repeated pinching up the nerve discoverd the furthest point at which the animals gave reflex movement (Fig. 1). Histological study confirmed that this gives a delicate test of the distance to which new fibres have reached, and a series of experiments at increasing time after operation showed that this margin advances down the nerve in a most clear-cut manner, at about 4·5 mm. per day after interruption of a nerve by crushing, and at 3·5 mm. per day after severance and suture. These rates are much higher than the 1 mm. per day commonly considered to be the rate of advance in man, though a few scattered clinical references,

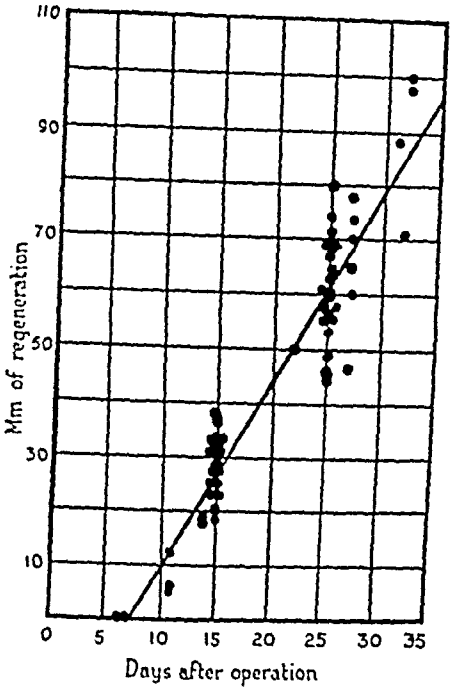

FIG. 1.—Distances reached by tips of new axons at various times after severance and suture of the tibial nerve of the rabbit, as measured by finding the most distant point at which a response is given when the exposed nerve is pinched (after Gutmann *et al.*, 1942). The regression line gives the rate of advance as 3·45 mm. per day.

especially to the progress of Tinel's sign down a nerve, have given comparable figures. We were therefore emboldened to hint that recovery after nerve injuries ought to be much faster than it usually is. This was very rash and even foolish of us, for the situation is too complex for any such simple statement to be true, though it does contain a large element of truth.

Soon experiments of rather longer duration began to yield estimates of the rate of regeneration measured by other methods. Thus the recovery of reflex spreading of the toes of the rabbit was studied after injuring the motor pathway at various distances from the muscle (Fig. 2), and also the spread of sensory recovery distally along a limb. The figures for rate of regeneration yielded by these experiments did not agree with each other or with those given above, though nearly all

were faster than 1 mm. per day. It became clear that what was being measured was not in all cases the same. In the experiments where reflexes were elicited by pinching the exposed nerve, we were measuring the advance of the finest tips of the fibres (presumably those responsible for conduction of pain). Such thin fibres, however, cannot produce function immediately after they have made contact with a muscle. Before they can do so they must increase in diameter and medullate at least to some extent. Where functional criteria of recovery were used we were measuring the advance, not of the tips of the fibres, but of a state of maturation of them to a level which we called that of

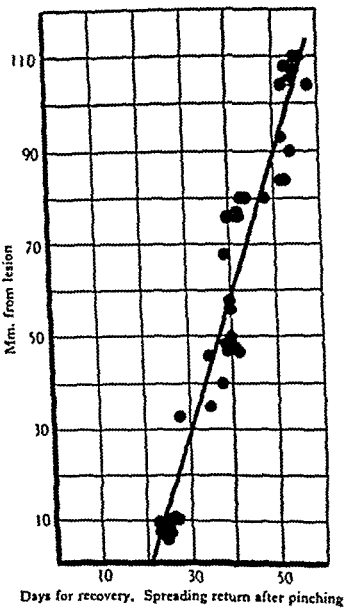

FIG. 2.—Times necessary for recovery of reflex spreading of the toes of the rabbit after crushing the peroneal nerve, which is the motor pathway for the reflex, at various distances from the muscle (from Gutmann *et al.*, 1942). The rate of advance of "functional completion" is 3·05 mm. per day.

functional completion. The advance of the margin of this state down the nerve is evidently slower than the advance of the tips of the fibres.

But here another possibility presents itself, namely that the degree of this maturation which is necessary for function varies with the length of nerve to be regenerated. Moreover, when a lesion is made far from a muscle or other end organ, that peripheral tissue will have undergone atrophy for a longer period than after a near lesion, and may take longer to recommence its functioning. It may well be, therefore, that the rate of regeneration will appear to fall off with time or with distance. In our experiments with rabbits little sign of this appeared, but Seddon, Medawar and Smith (1943), taking up the question in man with these ideas in mind, have found in some cases very distinct falling-off indeed. Here is a good example of the

interaction of ideas derived from experimental and from clinical work. Controlled observations can be made more easily in the rabbit than in man, and the study of the basic principles governing the rate of regeneration is therefore made more easily in animals. Extension of the observations to man shows that the same general principles are applicable but need modification, in this case because of the greater size in man, which makes him actually more suitable than laboratory animals for the study of regeneration of long lengths of nerve. Thus experiment and clinical observation supplement each other. But the difficulty which Seddon and his collaborators had in finding suitable cases for comparison illustrates well how hard it is to obtain exact answers to clinical problems, by reason of the diversity of human make-up and human accidents. They were forced to leave many questions doubtful, and it is still not possible to give any clear general picture of the rate of nervous regeneration in man. There is every reason to hope that such will be forthcoming from analysis of the cases now recovering. Such evidence as there is indicates that the tips of the axons advance as fast in man as in animals, namely 3·5 mm. per day after severance and suture. The margin of functional completion may advance down the nerve at a rate of over 2 mm. per day. Seddon, Medawar and Smith used the radial nerve for their studies, and were able to calculate in the same way the rate in a series of similar cases very carefully reported by Stopford after the last war. The rate of regeneration works out at three times as fast in 1942 as in 1919. The series of cases is limited, but we may hope that it will not prove exceptional. The result should give pause to the old-fashioned who hold that there is no progress possible in dealing with a simple type of surgery like that of peripheral nerves, and incidentally provides an excellent demonstration of the value of quantitative methods.

One of the most interesting results which has emerged from study of rates of regeneration is that all the processes of recovery are faster after a nerve has been crushed than when it has been severed and sutured. Histological study shows that following a simple crush there may be severance of the axons but not of the neurilemmal tubes in which they run. The newly formed fibres are therefore led back directly to their old end organs. But besides this better orientation there is also actually a faster progress of the fibres down the nerve, and a more rapid medullation. Seddon has applied the useful term axonotmesis to such cases of severance of the axon alone, as distinct from neurotmesis or severance of the whole nerve.

It is important in many ways for the neurologist and orthopædist to know how soon a nerve can be expected to recover in man; indeed, this should be the basis of his whole treatment and policy of operating if recovery should be delayed. But besides its immediate practical importance, knowledge about rate of recovery is also the basis on which comparison of various procedures can be made. And in

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particular we may return to the original question: does recovery proceed equally fast when suture is performed at varying intervals after injury? Clinical data on this subject are still very scanty, and it is one of our main hopes that more will soon be obtained. The answer affects the whole policy to be adopted in these cases. Since nerves make some recovery when repaired even one or two years after injury, there has been a general tendency to delay operation. This policy grew up during the Great War partly from the fear of sepsis, partly from the consideration that in the majority of nerve lesions the nerve is not fully divided and therefore some recovery may be expected.

Holmes and I (1942) studied the question experimentally, joining severed nerves in rabbits after periods of delay as long as eighteen months. The experiments were arranged so as to estimate separately

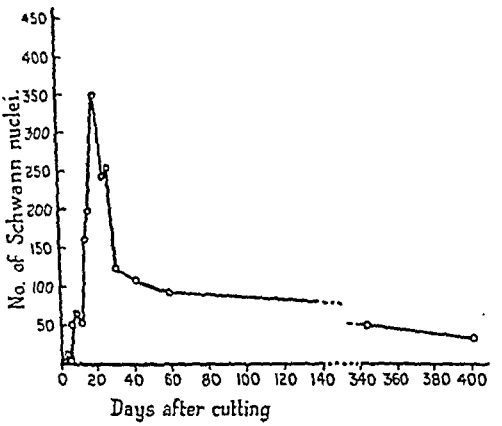


FIG. 3.—Numbers of Schwann cells produced by explants of nerves made from peripheral stumps which have been left uninnervated for various times. Ordinates, number of Schwann cells wandered out per mm. of explant (after Abercrombie and Johnson, 1942).

the *vis a tergo* or power of outgrowth of the central stump, and the *vis a fronte* or receptive power of the periphery. We found that, with the progress of time, the former abated little, but the latter fell off considerably. Various factors contribute to make the process of regeneration less complete when suture is performed after a considerable delay. The actual union of the stumps becomes less good, and this may be because of a falling off in the activity of the Schwann cells, which emerge from the peripheral stump and grow towards the central (Fig. 3). Once in the peripheral stump the nerve fibres travel in tubes left by the old neurilemmal sheaths and filled with the protoplasm of the Schwann cells. In a nerve stump left uninnervated for a long time these tubes become gradually obliterated by collagen. Professor Learmonth was good enough to send me some pieces of nerve from a leg which had remained denervated since the last war. The connective tissue had increased in this nerve to such an extent that the tubes had been largely obliterated (Fig. 4), the Schwann cells

being reduced to fine fibres (Fig. 5). New nerve fibres growing into such a stump can mature only slowly and imperfectly, and Holmes and I found that even a year after late suture in rabbits medullation was much less perfect than in a control nerve which had been sutured immediately.

While these very long and laborious experiments were proceeding, Dr E. Gutmann and I (1944) developed another line of attack on the same problem by studying the recovery of muscles which had been left for various periods without nerves. We found that the atrophy which occurs in a denervated muscle is progressive, and nerve fibres returning to such a muscle find a very different situation according to whether it has been left for a long or a short time. The progressive shrinkage of the muscle fibres, and the fibrosis between them, makes it more and more difficult for the nerve fibres to reach the muscle fibres, and the recovery of many muscle fibres is first delayed then finally made permanently impossible. Actual disappearance of denervated muscle

FIG. 4.—Bundles of posterior tibial nerve which has remained uninnervated for 26 years. Masson's stain. The nerve is reduced to a mass of collagen containing a few Schwann cells and fibrocytes. ×130.

FIG. 5.—Longitudinal section of the same nerve as Fig. 4. Holmes' stain. The Schwann cells are reduced to very fine strands by the shrinkage of the walls of the tubes in which they run. These strands may show a remarkable similarity to nerve fibres. ×1220.

FIG. 6.—Fibres from peripheral stump of rabbit's nerve cut three days previously and stained with osmium tetroxide. The myelin is breaking into long ovoids between which neck droplets ("Plateau's spherules") can often be seen. ×260.

fibres occurs only very late and was still proceeding in the muscles of Professor Learmonth's case, which had been denervated for twenty-six years.

Several different lines of evidence therefore point to the probability that recovery will be less perfect if suture is long delayed. As I say, we have as yet only very imperfect data as to how important this factor may be in man. The curve of decline in regenerative power may be less steep than in the experimental animals; it may be more so. The function of animal experiments in such matters is to point the way to clinical probabilities, which must then be tested directly. Thanks to the anti-bacterial agents now available, surgeons have been encouraged to operate earlier on injured nerves, though this policy has been very slowly adopted. The peculiar situation in the North African campaigns made it difficult for any such change to be introduced. However, the possible advantages of early operation in suitable cases are now widely considered, and we may hope that some of the casualties suffering nerve injuries in the present conflict will obtain considerably better recoveries than in the past.* But it must be stressed that

* One qualification must be mentioned, namely, that there is some evidence that suture of a nerve immediately after it has been severed gives somewhat less good recovery than suture a week or two later. Again, however, one must emphasise the need for really satisfactory data to demonstrate the full curve and enable us to determine the optimum time for operation.

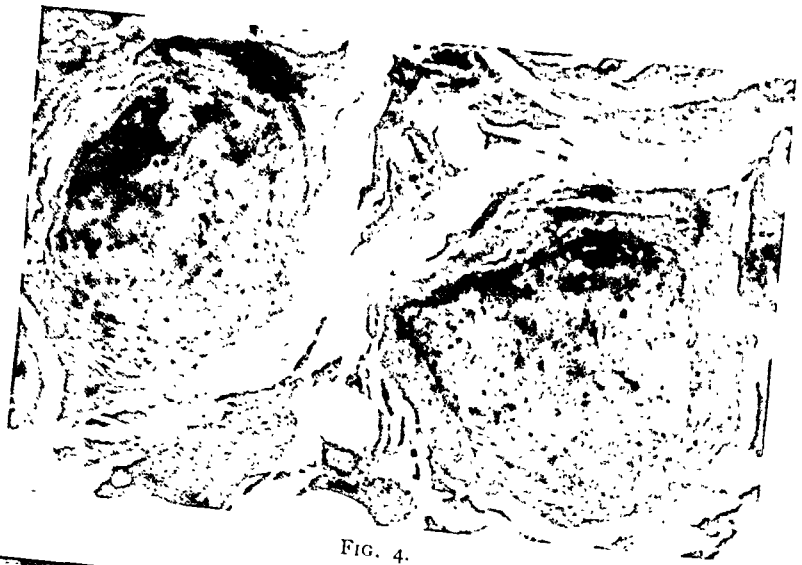


FIG. 4.

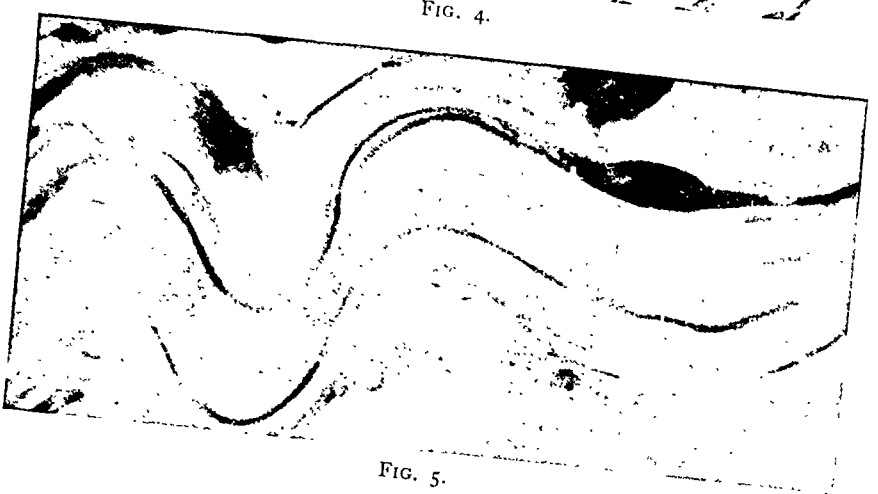
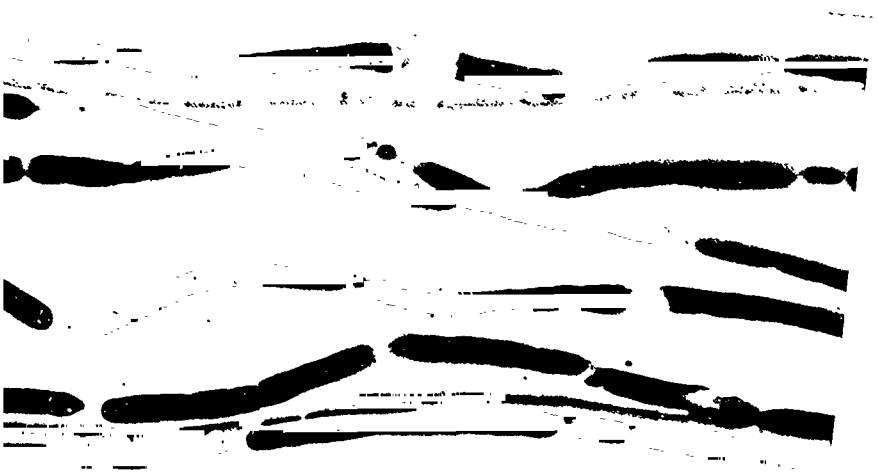


FIG. 5.



there is no certainty of this, nor indeed any satisfactory data on the subject in man. It is most important that these should be obtained to provide a sound basis for surgical policy. The task will not be easy, since it is necessary to obtain series of cases differing only in a single variable, say level of lesion, or time between injury and operation. However, even rather small numbers of *carefully selected cases* would provide more useful information than massed statistics of hundreds of cases with all the variables intermingled.

So far I have dealt in detail only with item i. 1 of the list of problems drawn up in 1939. This, and the problems which have developed out of it have been followed in especial detail because it illustrates the interweaving of clinical and experimental work. It would be impossible to follow out the remaining headings equally, for there were twenty-two of them and many have been added since. i. 2 the question of the effect of age on regeneration, was not pursued experimentally because it seemed unlikely that experiment could suggest any effective procedures for putting the clock back in this respect. i. 3 concerned the putting out of many branches by central axons: is this a desirable factor and can it be influenced? We still know very little of this, but recently have discovered that if all these branches are allowed to proceed down the peripheral stump but prevented from reaching an end organ, then all remain present but small. However, any one branch that makes contact with an end organ increases at the expense of the others. This peripheral influence is a very powerful one on the maturation, but how does it work? i. 4 concerned the effects of temperature, massage, vitamins and other treatments on regeneration, and we have not pursued it very actively. It seems at first to offer prospects of success, and is indeed the basis for work usually suggested by anyone unfamiliar with the subject. But we felt that with no hypothesis to work on we were unlikely significantly to speed the regeneration. Workers in America have failed to find any such acceleration with vitamins and other agents. On a somewhat similar theme, however, namely methods of preventing the atrophy of muscle, E. Gutmann and L. Guttmann (1942) have demonstrated that the wasting of a denervated muscle can be delayed by galvanic therapy, and this has been confirmed by others, though there is still doubt as to the best procedure to be employed. Besides more experimental work on the electrical side, clinical studies, again, must take the matter up.

i. 5 was the study of negative regeneration: how to stop the formation of neuromas in amputation stumps, etc. L. Guttmann and Medawar (1942) tried the effect of many agents and showed that alcohol, so often used for this purpose, is less effective than others, such as formaldehyde or gentian violet. Apparently these experiments have hardly been made use of as yet by surgeons, perhaps because formol is not a pleasant reagent to use in the body; I do not know why gentian violet has not been adopted.

Ritchie (1944) has studied the electrical excitability of recovering muscle and produced an instrument for testing it from which very much is hoped.

Obviously, since recovery of function is the aim of nerve surgery, it should also be the object of experimental studies. Indeed, one of the most interesting and earliest extensions of our programme was that which involved the use of functional criteria for the measurements of rates of regeneration. Others such as Sperry (1943) have used experimental methods to study the possibilities of readjustment of function of wrongly connected fibres, possibilities which they find to be distinctly limited. Yet in spite of continuous attempts to keep functional problems before us, the method of analysing the problems of nervous regeneration into a series of stages has tended to make us neglect the action of functional factors. It is convenient to consider each stage of regeneration separately, but this may make one neglect a later functional influence which overrides all previous ones. A good example of this has been the study of the factors which affect the size reached by regenerated fibres. After making laborious experiments to prove that both the size of a parent fibre and of the peripheral tube in which it runs influences the diameter of new fibres, we now find a much more potent influence. A nerve fibre which makes contact with muscle at the periphery becomes much larger than one which fails to do so. Perhaps we should have expected this, but it is interesting that it came as a surprise. It remains, of course, to find how the effect is produced.

It is the business of the basic scientist to try to analyse phenomena in such a way as to show the connections between them. To show the regular sequences and patterns of behaviour which we characterise as the results of the operations of forces. In doing this it is natural, if not wise, to tend to oversimplify even to the extent of neglecting aspects of the subject, such as the functional, which are of great importance. The task of discovering relations is hard enough in any case. It might be said that the function of the clinician in this dialectical process is to correct the tendency to over-simplified general ideas. The clinician, necessarily in touch with *all* the aspects of human physiology, can force the neglected ones on the attention of the physiologist. In this sense it is he rather than the experimentalist who is the pioneer, journeying out from the ordered civilisation of science into the varied and mysterious wilderness of living phenomena. With this experience he should be continually reminding the theorist and experimenter of the extent to which their complete schemes fail to cover all the facts.

But in any well-ordered body of knowledge there must be general theories, describing the forces which operate to produce the phenomena observed. One comes back continually from the study of practical problems such as when a damaged nerve should be explored, and mysterious and intriguing ones such as what enables the periphery to

influence fibre diameter, to the need for a general theory of nervous regeneration. This in turn involves a knowledge of all of the factors which maintain a nerve fibre intact. And, historically, we have found throughout that while attending to the special problems mentioned above, we have been repeatedly turning back to the fundamental questions, " what is a nerve fibre ? " and " what forces are at work to maintain it and to make it grow ? "

During the last year I think we have proceeded some way towards answering these questions too. A nerve fibre is a very long cylinder of flüid or semi-fluid nature. Now anyone who has tried to apply a smooth coat of varnish to a wire, or looked at the drops on a spider's web, will know that surface tension tends to divide a long liquid cylinder into a series of drops. In a nerve fibre there must be some force preventing this, and the force must come from the cell body, because when a portion of nerve is cut off its " degeneration " consists in just such a breaking up into spherules (Fig. 6). The form which they adopt during the process, large drops with smaller ones between, shows most clearly that it is chiefly a result of surface tension.

The normal maintenance of the cylinder, I suggest, depends on a turgor pressure within the fibre, originating from the nerve cell body. It may seem strange to consider a nerve fibre as a turgid fluid, but there is considerable evidence that it is correct. The material of the very large nerve fibres of the squid is so liquid that it pours out freely if the fibre be severed, and if one wants to take out one of these nerves to study its action potentials, it must first be ligated at both ends. We do not know whether the flow within a nerve fibre is at all fast or active ; it may be very slow indeed. But it is sufficient to cause considerable swelling and outflow of liquid from the central ends even of mammalian nerve fibres during the days immediately after they have been severed. I suggest that it is also able so to inflate the normal nerve fibre as to allow it to maintain its cylindrical shape, in spite of the tendency of surface tension to produce " degeneration."

Here, then, we have the outlines of a general theory of nerve maintenance and regeneration. We must look for and measure the forces which produce turgor and outflow of the axon, for the conditions under which the material is able to spin new fibres along suitable surfaces. This may tell us much about the influences affecting rate of regeneration, number and direction of branches and so on, though it is certainly difficult as yet to see how it agrees with the hypertrophy produced by connection of nerve with muscle. With knowledge of the forces at work in a nerve we shall begin to obtain a unified general picture as a basis for our neurology. In this way we link it with physics and other sciences and obtain all the advantages of generality. At the same time we bring into view the possibility of really great advances in technique. It is useful to find out " practical " things, such as how much a nerve can be stretched, or when to operate, but

if we spend our time on the "theoretical" questions of the forces operating in a nerve, who knows how far we may go towards preventing its degeneration or speeding its regeneration?

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DIAGNOSIS AND DESCRIPTION OF CANCER

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3. *Classification and Nomenclature.*—Classification and nomenclature are closely related. The names of tumours should naturally be based on orderly subdivisions or classes and should be defined as far as possible by those names. This is a great saving to the memory, and might easily follow the method of the biological sciences: with families, genera, species and varieties. We may still adopt the principles laid down nearly a hundred years ago by Virchow and his predecessors, which has been followed with much consistency ever since. They were based on histology and embryology and received baptismal authority in Virchow's (1855) phrase, *omnis cellula a cellula*, and to some extent with the important addition, *ejusdem naturae* (Bard, 1886).

Primary nomenclature for everyday use would be of genus-species type on a strictly binomial system (Linnaean system). A rather strict adherence to such a system is observed by botanists, zoologists, and bacteriologists, and it is undoubtedly a good system if for no other reason than its uniformity. Its application to tumours should be even more strict than in the biological sciences, for there is little else required than a cell or tissue basis for species naming, and the number of species is comparatively small. Mallory (1914) put them as about fifteen. Supplementary description and, when possible, compound description such as fibroadenoma, neurofibroma should be avoided, and the genus or species of the tumour restricted to the essential, answering in the name itself not only the question of what the tumour is (*quid sit?*), but also what sort of thing it is (*quale sit?*).

We have begun here with nomenclature before classification, and I may refer to tentative proposals which I submitted (Harvey and Hamilton, 1930) for certain names. These proposals replaced the names of carcinoma and sarcoma by the termination -blastoma, leaving that of -cytoma for the corresponding benign types; fibroblastoma was a fibrosarcoma and fibrocytoma the simple fibroma. Mallory had used the termination -blastoma only. One or two anomalies of naming deserve special reference, and I should make a plea here for the restriction of the termination -oma to tumour growth. It is a matter of regret, I think, to see terms like tuberculoma, syphiloma and amœboma coming into use. The procedure seems to me a reversion to the old and unspecific use of the word " tumor " as simple swelling, while a name like " granuloma " is really misleading; an

older name, indeed, " phlogoma," with its reminder of " phlogiston " might claim priority over granuloma. I doubt if hæmatoma and atheroma could be discarded, but cholesteatoma and xanthoma could easily be dispensed with. It is obvious, too, that an eponymous nomenclature would have no place in this system. Such tumour namings, at least, could only be admissible as temporary expedients; they are exemplified in the use of names such as Wilms' tumour, Grawitz's tumour and Ewing's tumour. A name, for example, such as Pick's disease is meaningless, if only that there were several Picks and several corresponding diseases. We shall see, in considering the principles of classification of disease as applied to tumours that there is no objection to the introduction of naming by cell, tissue or locality and to their elastic use, but such namings must still be on an unmixed basis. Group, variety or type subdivision may give us names or epithets of useful application such as histiocytic and lymphoblastic, even if we do not adopt the generic terms of histiocytoma and lymphoblastoma. Now I should beg of you not to dismiss this argument as mere word-spinning or exercise of pen and ink. The whole idea of the argument is insistence on precision in describing cancer, and it is not extravagant to maintain that naming should be precise. The difficulty of naming must have presented itself to every practising pathologist. You and I are identified to a large extent by our names, usually by binomials. The system I advocate, therefore, is scarcely to be regarded as only a new set of labels of an arbitrary and upsetting character. We should not say with the Blimp, " This thing is new, take it away," nor yet, " This thing is old, it must be wrong." It would be necessary, however, to recognise that any change in the naming of tumours should be gradual and be adopted by general consent, with intent to make diagnosis, and description more efficient and precise. The more nearly the naming defined the object the easier would such a change become.

Classification is another subject for discussion in the diagnosis of cancer. I still find that the principles of logical classification in pathology laid down by C. W. Cathcart in 1896 are as valid and necessary to-day as they were when issued, and nearly as often still transgressed. The principles were merely well-known canons of logic, and are set out as: (1) the constituent species must exclude each other; (2) the constituent species must be equal when added together to the genus; (3) the division must be founded on *one* principle or basis. It is the first and third of these rules which are ignored in many medical classifications. The classes into which cancers are subdivided, regarded as species, should be mutually exclusive and the basis of classification used within groups, genera, species, and types should be one, not manifold. The bases commonly used for classification of disease are reducible to three—locality, result and cause. It is the mixture of these bases which must be avoided if the classification is to be scientific, logical and understandable by the student or the

practitioner. In the case of cancer, with a still unknown causation, locality and result are the only two left, and are very apt to be mixed. An example, not wholly fictitious, of the small section of malignant epithelial tumours of the kidney, which includes the duct with the organ, might be: (1) adenocarcinoma, (2) hypernephroma, (3) embryoma, (4) squamous epithelioma. Here we could disentangle the classification to give a satisfying dichotomy, but as it stands it is mixed and includes as bases—cell, tissue, organ and embryology. Recent classification systems largely avoid the error. Classification of cancers, however, is a difficult matter. A use of the word " other " to gather up the unclassified tumours into the universe of genus or species is both logical and legitimate. It has been utilised in the recent Medical Research Council Classification of Diseases (1944).

4. *Statistics.*—The mention of statistics may conjure up a vision of irksome entries and returns, or even of forms in triplicate. It is very easy to get used to these, and they represent, as a rule, some saving of labour for somebody. They can be, and often are, constructed to save labour of writing and to require no more than a tick or stroke to give the necessary information (Harvey, 1929), *e.g.* married: ✓, single: ; male, female. Punch systems are now extensively used for records. As a mode of record I have a long-founded preference for the use of square compartments, and number entries with code indices for their interpretation. But apart from such considerations as economy of time and labour, it should be regarded as a contribution to science and a community service to furnish written detail of the main facts of a case to the pathologist engaged on the diagnosis of cancer, just as it becomes in turn the duty of the pathologist to make appropriate statistical record of the data. Most of all, I think, should a careful record, or as careful a record as possible, be made of the sequel in a cancer case. It is the chief check on the correctness of the diagnosis and is the concern of pathologist, radiologist and surgeon alike. How often the pathologist finds that he can get no record of the outcome of a case which he considers scientifically important, or which has been subject of disagreement, or in which he is personally interested. The follow-up is perhaps a burden. It is fortunately realised now how important a datum this is, and many hospitals have established an assiduous inquiry system. I put up the plea, therefore, for submission of full essential data in all cases to the pathologist and for close attention to and record of sequelae. I should hesitate to put forward any suggestion for increasing the burden of the student, but it seems to me that it would not be out of place that he should receive some instruction in the modes of presentation of case data in statistical form, such as the use of the frequency distribution, dispersion about the mean and its measure the standard deviation, the mean and the mode, the statistical significance of a difference, and finally the method of setting out a correlation coefficient table or table of double entry. The medical man is occupied, in making a diagnosis,

in estimating a probability. It has become more and more obvious to me, in practice, that this aspect of diagnosis as a probability, the chance of occurrence, is not sufficiently realised and requires to be emphasised.

The use of the diagnostic data which he has collected will sooner or later present itself to the pathologist. It does indeed present itself to him consciously or subconsciously in all his judgments. I should say that perhaps the biggest pitfall in this utilisation is the entry of selection into the question. The use of the word "selection" has a slightly different connotation to the statistician than to others. The statistician has always to be on the look-out for selection, unconscious usually, but representing the factor which may be operative in a given deduction. Hospital statistics, autopsy statistics, experimental and laboratory statistics, radiological and surgical statistics are all highly selected and must be examined carefully on this count. To take a very crude example, it would not follow because I diagnose bronchogenic carcinoma or deal with the causation of sterility most frequently from Newcastle, basal cell carcinoma from Kansas City, U.S.A., tumours of the brain and breast from Edinburgh, that these are necessarily attached to these localities in a geographical, topographical or population sense. Selection, therefore, militates to a very great extent against the usefulness of deductions even from large data, which may not apply to any real cross section of the general population. The duty of collection and record of cancer statistical data will devolve, as a service to the community and to science, first upon the general practitioner. It is he who sees the little lumps, that are so important. Again, it should not be the attitude of the surgeon that the follow-up is not his concern even if he is satisfied that, operatively, he has done his best for his patient. Medicine, it must be contended, is as much, or even more, a science than an art. The pathologist should not complain of routine duties. Routine material is just about the best raw material for research, and especially statistical research, at least in relation to the human being. Many of the secrets of pathology are to be sought in the daily presenting specimen. We still need to have much diagnostic, microscopic light shed on questions of benign and malignant character, radioresistance, radiosensitivity, alteration of normality with age (geriatrics), etc. The daily specimen regularly poses these questions, and the answers, if obtainable, are worth a systematic statistical record. The follow-up of cases and the regular transference of the information to the pathologist will help to provide answers to many such questions. The pathologist must be incorporated, with the clinician and the radiologist, as one member of a scientific body and not left to pursue his research alone.

The practical application of methods of statistical approach to cancer and its problems merits some attention. Most of us have at one time or another tried to bring statistical proof for, say, some diagnosis or treatment. I have now for a long time advocated the

strict " alternate case " method of approach and have been variously called by colleagues or fellow-workers—inhumane, procrustean, and so on. I mean, too, by the alternate case method a strict procedure, not that of comparison with previous results, by alternative hospitals, wards or individuals, but the use of one and the same population. One of the opprobrious epithets directed to that procedure is the word " experiment "—human experimentation. I always myself use the word " trial " instead of " experiment," and I contend that trial of rival methods with some prospect of arrival at clarity is essentially *both* humane and scientific. At all costs one must avoid, as I have already said, the element of selection of our cases: the selection of those suitable for our special treatment, the primary sorting out of the operable from the inoperable, the separation of those cases which can be usefully treated from those that would be—in the opinion of the operator—wastefully treated. At least if, occasionally in ordinary common-sense, we must adopt such a degree of selection, it ought to be carefully sought out and placed on record. This, then, is an aspect of the statistical investigation of cancer which must be " described " to student, practitioner, specialist and general public. Prejudice has to be overcome to so-called, wrongly called, " experiment."

III. Description

1. *Descriptive Method.*—Description of cancer implies communication of verdict or views to another: to the pathologist by clinician and *vice versa*, to the student, scientific society and general public. I may take in the first instance that with which I am chiefly engaged, the description in report of the microscopic appearances of freshly operated-on material. The principles involved in such a report are: (1) It should be understandable; it should give, if possible, at least a diagnosis and in ordinary language. At the same time I feel it is necessary to insist that there are occasions when the clinician should be content with the answer from the pathologist of " I do not know," or allow him without demur to reverse his previous conclusion. A remark made to me in correspondence by a noted radio-physicist came in substance to this—pathologists, radiologists and clinicians seem either to use the same terms for different things or different terms for the same things. That makes one realise the necessity of frequent combined conferences.* (2) It should have scientific as well as clinical value. (3) An ideal report on cancer should contain diagnosis,

* I look on the differentiated cell in tumours as finished and of no consequence for the radiologist except as possibly obstruction to his beam; I regard the real radio-sensitive and real tumour cell, for radiologist and surgeon alike as the embryonic stem cell; I should think that in this sense all tumours are radiosensitive, and that obliteration of *this* cell by burning or killing is the essence of radiology, and that *its* removal is the basis of surgical intervention. In such a view, which is not new, I believe also lies the morphological key to tumour growth and to the nebulous distinction in growth and causation between benign and malignant tumours.

differential diagnosis, contradiagnosis and negations (such as, say, absence of tuberculous or syphilitic infection), with the inclusion for scientific record even of the apparently non-significant appearances. (4) I prefer the syllogistic method of reporting, only, of course, with more than the simple major and minor premises. (5) No rubber-stamp reporting is admissible. (6) Additional remarks may be desirable: on possible degree of malignancy, radiosensitivity, complicating phenomena such as sepsis, operative clearance of the tumour area, and even the gentlest of reminders that information has not been supplied on questions such as: What was the Wassermann reaction, and what did the blood examination show? In specially interesting cases I should add, on occasion in my report, references to the literature. Most of this applies, of course, to laboratory reporting from a distance, as the best means of establishing co-operative contact with the clinicians. As far as I can see, moreover, cancer reporting in the future will require centralisation rather than decentralisation, if the benefits of the Cancer Act are to be as widely diffused as possible. There should be no difficulty about devising a centralised laboratory system which provides for frequent visitation, but outward as well as inward.

I have advocated, for reporting, a syllogistic or deductive approach to the verdict, the approach from base to apex of the diagnostic cone. It may be more artistic to approach the conclusion by steps which are plainly factual and not tendentious. We are not, however, concerned wholly with formal presentation, and there is much to be said for commencing the report with the diagnosis. I remember, for example, how a surgeon once described to me the way his patient's face lit up (the patient was a doctor) on hearing the first sentence of the report—There is "no evidence of malignancy." That, of course, was statement of conclusion. This may then be followed by relative detail, scientific record and unexplained features.

Description of cancer I have said is not merely from pathologist to clinician, but, in reverse and initially, from clinician to pathologist. It needs emphasis, too, that the data of age, sex, size, site and symptoms of tumour growth, with many others, are all of the utmost use to the pathologist if his report is to be a truly reasoned one; otherwise it is apt to be bare.

There is one method of description for which I have long had partiality and used for my own notes, but have not dared to put into official use. It appealed to me long ago and made use of what was then the Bertillon system of identification of criminals, soon to be replaced by finger print identification. In this Bertillon system the use of qualifying phrases of indefinite type was discouraged; it was not permissible to use terms like "slight," "rather," "somewhat," "fairly," "tendency towards," "suggestion of" and so on. The qualification of an adjective was by bracketting, double bracketting and treble bracketing for the *diminuendo* series and underlining in

the same way for the *crescendo* series. Thus without resort to numerical units, which will always be desirable, size in all its conceivable degrees could be set out by using one or other of the terms: small, medium and large—(((small))); ((small)); (small); medium; large; large; large, as seven gradings. Again, three gradings of "congestion" could be set out as: (congestion); congestion; congestion.

2. *Teaching and Instruction.*—Teaching involves description, and in sequence it is the medical student who receives the first, the expert teaching, and the patient who receives the last, the advisory teaching. The student is the pre-practitioner, and he should be well drilled in the conception of the pre-, or primary, cancerous state. He should be made to realise that cancer diagnosis must be early and that, early cancer being curable, early diagnosis and early action are the best curatives of cancer. The general principles of treatment of cancer by surgery, radiation and chemotherapy require co-ordinated instruction, and so we come naturally to the suggestion of one more burden to the medical curriculum, the lectureship or the professorship of oncology. Perhaps that would be best dealt with as a post-graduation study. The practitioner should realise thoroughly the importance of oncoscopy: ὄγκος means mass, bulk, lump, tumour, weight and, metaphorically, difficulty, trouble and dis-ease. It is the general practitioner who will inspect the little lumps, become suspicious and take curative action. With our arrival in sequence already at the practitioner we embark upon the practitioner-patient relationship and—we need not delay the topic—that of propaganda. Opinion seems steadily turning to the necessity of more propaganda directed to the understanding and detection of cancer. My own feeling is decidedly in favour of systematic, periodic examination for the earliest development of cancer and the scrutiny of all tumour-like growths; cancerophobia has been paraded as the bogey. I do not think I should go quite as far as to advocate that every woman over thirty should be taught to examine her own breast not less than every month.

The teaching of the student, who becomes in due course the resident medical officer of a hospital, must include the mode of despatch of cancer material and the type of information to be rendered to the pathologist; that that information should be as full as possible is a fairly safe generalisation. Such full information must not on any account be regarded as creating bias.

Biopsy diagnosis affects the specialist surgeon and he—as a medical student—will, or should, have been taught the importance of obtaining material to a reasonable depth, to include the growing edge as well as the more diagnostic interior lesion, from a well-selected, even if necessarily small, piece of tissue. Particular areas for microscopic examination should be marked before despatch to the laboratory. New hospital residents succeed each other. Printed rules for the despatch of material (Hay, 1945) to the pathologist should be available

for each new resident. I do not see any such sets of rules given in any appendix in any systematic text-book of pathology that I know. An appendix on biopsy method would be valued and valuable. One other recommendation I should make: Teach your technician, not technique, but diagnosis. The labour will be repaid; it will in time ensure a valuable second opinion.

3. *Inheritance.*—The inheritance of cancer or a cancer tendency is a subject which is certain to be broached, and the practitioner asked for advice. It is a difficult one, but at least the advice may be reassuring. Much experimental work has been done on cancer inheritance in mice, and quite definite cancer and non-cancer strains have been produced. The method used, however, to produce the strains is of an extremely artificial kind: selection of a particular strain and a brother-sister or parent-child mating. These are calculated to produce recessive gene strains in an almost pure form. Most authorities seem inclined to regard cancerous phenomena in human beings to be dependent on recessive factors in the mendelian sense, which could only, as in mouse cancer strains, be intensified by a combination of inbreeding and selection. Some tumour conditions such as neurofibromatosis may be of the order of dominant characters, but this is probably an exception. In fact, there are few serious defects which are carried by dominant genes. In the human being no concentration of cancer susceptibility comparable to that in these special mouse populations can occur.

Many, if not most, insurance societies appear to ignore a cancer heredity, probably for a very good reason. Cancer is to a very large extent a late-in-life phenomenon, and to that extent of less importance. Possibly the insurance societies know, or at least argue, that cancer in the progeny of cancerous parents may be, in part at least, a spurious correlation due to the fact that the children come of parents with a natural expectation of long life, of living to old age, of living into a cancer age. The children in that case start with the expectation, by inheritance, of living to an old age, which should not be penalised in the insurance premium, even if it does mean ultimate death from cancer. Part of the present day supposed increase of cancer may be, and probably is, due to increased expectation of life.

Contrast now, for the sake of example, another condition, and consider it from the standpoint of gene mutation. Sufferers from xeroderma pigmentosum, one of the inherited skin conditions, usually die of cancer under the age of fifteen years, that is under the reproductive age. The condition ought, then, to disappear altogether by weeding out the carriers of the gene and, as it does not, there is argument here for an independent gene mutation. This weeding out would be complete and prompt if the gene were dominant, but very slow if recessive. Somewhat similar reasoning applies to the non-cancer condition known as erythroblastosis fœtalis, with its Rh factor.

In the case of the common cancers according to Haldane (1942),

probably a number of genes are concerned in the production of susceptibility. That would make inheritance of cancer very complicated and, perhaps, quantitative rather than qualitative. From the social and economic point of view a disease which tends to kill at old age is not of the same importance as that which has an earlier age incidence.

In conclusion of this brief reference to inheritance, I may say that too little is known on the inheritance of a cancer disposition in the human being and of the relative rôles of inherited and acquired causation, of nature and nurture, to be dogmatic on the subject.

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NEW BOOKS

A Handbook for the Student Health Visitor. By EDITH WILD, S.R.N., S.C.H., R.S.I. Pp. vi+66. London: H. K. Lewis & Co. 1944. Price 3s. net.

This little book is intended to convey to the student health visitor the essential differences between curative hospital nursing and preventive public health nursing. It describes the aims and nature of the work, its difficulties and disappointments, its value and its successes. Miss Wild considers the equipment necessary for this work to be knowledge, sympathy and long patience and explains her reasons for this opinion.

The book is full of helpful advice and good counsel and should prove of the greatest service to those for whom it is intended.

Catalogue of Lewis's Medical, Scientific and Technical Lending Library. Pp. viii+922. London: H. M. Lewis & Co. 1945. Price to non-subscribers 25s. net.

Messrs Lewis have issued a new edition of their catalogue, revised to the end of 1943. It consists of two parts; the first gives the titles of the books available, classified under the author's name; the second part is arranged under subjects so as to facilitate reference. The catalogue will be of great use in showing what literature is at present available in the various fields of medicine and allied sciences.

Reconstructive Surgery of the Eyelids. By WENDELL L. HUGHES, M.D., F.A.C.S. Pp. 160, with 198 illustrations. London: Henry Kimpton. 1943. Price 21s. net.

This monograph was originally presented as a thesis for admission to the American Ophthalmological Society. It deals with the repair by plastic surgery of deformities of the lids arising from injury or surgical interference. Of the ten chapters the first eight are historical, and the author traces the development of reconstructive lid surgery from the seventeenth century onwards. All forms of skin grafting and reconstructive operations are reviewed, including various methods of restoration of the tarsal plate and the transplantation of hair-bearing skin to form new eyelashes and eyebrows. The ninth chapter deals with the author's method of blepharopoiesis (lid construction), and the tenth contains a description of some cinematic films used as illustrations. The text is excellently illustrated and a bibliography of 451 items is appended. The book will be of value to those who are interested in the plastic repair of the eyelids.

What is Tuberculosis? By M. SEKULICH, M.D. Pp. vii+96. London: William Heinemann Ltd. 1944. Price 3s. 6d. net.

Dr Sekulich, a Belgrade physician and specialist in tuberculosis, writes with a profound knowledge of his subject. His book is intended for the general public, but contains much that is of interest to the medical man. It gives a general account of every aspect of tuberculosis, including the measures necessary for its control and eradication. Tuberculosis is not merely a medical problem, but one for every member of the community, and the struggle against it will demand the fullest resources of the State.

NEW EDITIONS

The Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D. Third Edition. Pp. 934, with 798 figures and 6 coloured plates. London: Henry Kimpton. 1944. Price 50s. net.

The present edition of this useful text-book is much enlarged by the addition of new matter and new illustrations, many of which are from photographs. Although, as is pointed out, no attempt has been made to make the book encyclopædic, a large number of operations are described, some because the author does them himself, others because he regards them with approval. The author has not confined himself to descriptions of operative technique, but has discussed each subject extensively; for example, nearly 150 pages are devoted to plastic surgery and the eyelids, 80 to cataract and 100 to glaucoma. Certain sections have been contributed by recognised authorities in their own spheres, such as that on keratoplasty by Castroviejo. The chapter on muscles has been expanded and partly rewritten. Wherever it has been considered desirable, anatomical, physiological and pathological conditions are discussed. The new edition provides an excellent and up-to-date reference work on ophthalmic surgery.

A Textbook of Pathology. Edited by E. T. BELL, M.D. Fifth Edition. Pp. 862, with 448 illustrations and 4 coloured plates. London: Henry Kimpton. 1944. Price 45s. net.

The authors have furnished the medical student with a text-book in which the pathological lesions are correlated with the clinical manifestations of the disease. Much new material has been introduced and many topics of interest in war medicine, such as shock and blast injury, are discussed more fully. Vitamin deficiencies are dealt with very extensively, and the subject of sarcoidosis is discussed at length. The authors have brought the text into accord with current medical opinion, and the references to the literature have been carefully selected. The book is written clearly and concisely and the illustrations are excellent. The student will find this book of great value during his clinical training and an excellent introduction to medicine.

A Pathology of the Eye. By EUGENE WOLFF, M.B., B.S. (LOND.), F.R.C.S. (ENG.). Second Edition. Pp. vii+285, with 212 illustrations. London: H. K. Lewis & Co. Ltd. 1944.

This valuable and useful work has won a place for itself in ophthalmic literature which will be enhanced by the new edition. The text has been largely rewritten and some of the clinical material omitted in order to enable more attention to be given to morbid histology. Although over eighty new illustrations have been added, many from the author's own preparations, which add greatly to the value and interest of the text, more might still be added with advantage in certain sections. The new edition is assured of a warm welcome from all ophthalmologists and will be of special value to candidates for higher qualifications.

Murrell's What to do in Cases of Poisoning. By H. G. BROADBRIDGE. Fifteenth Edition. Pp. vi+190. London: H. K. Lewis & Co. Ltd. 1944. Price 8s. net.

The first edition of this book appeared in 1881, and since then it has been frequently revised and brought up to date. The present editor, who is a coroner, has re-written the section dealing with the legal aspect of cases of poisoning.

This handy book is full of practical and useful information.

The Students' Pocket Prescriber. By DAVID M. MACDONALD, M.D., D.P.H., F.R.C.P.E. Twelfth Edition. Pp. xvi+348. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 7s. 6d. net.

The twelfth edition of this practical volume has been brought up to date with all the recent advances in therapeutics and medicine. The art of prescription writing is slowly acquired, but the student and newly qualified practitioner will find this manual of great material benefit.

Illustrations of Bandaging and First Aid. By LOIS OAKES, S.R.N., D.N. Third Edition. Pp. vii+276. Fully illustrated. Edinburgh: E. & S. Livingstone. 1944. Price 6s. net.

The present edition of this useful little book has been revised and enlarged. The greater part of it is devoted to bandaging, but there are sections on dealing with shock, hæmorrhage and fractures, and on how to remove a patient. Short clear descriptions are given, and these are illustrated with 300 well-taken photographs. A small coloured supplement shows pictures of recent war wounds.

This excellent book should be of the greatest service to nurses and students.

Handbook of Physiology and Biochemistry. By R. J. S. MCDOWALL, M.D., D.SC., F.R.C.P. (EDIN.). Thirty-eighth Edition. Pp. xii+898, with 305 illustrations. London: John Murray. 1944. Price 25s. net.

In the thirty-eighth edition of this book, previously known under the editorship of Kirkes and of Halliburton, Professor McDowall assumes sole responsibility. Reduction of histological description and of the blank note pages has allowed revision and extension of the text and addition of 80 new illustrations. The book provides an adequate and up-to-date survey of Physiology—we regret the omission of the histology which made the picture complete in earlier editions—and will be deservedly popular with medical students, for whom it has been largely intended.

A new feature has been added in a bibliography of literature for more detailed reading; numerous references throughout the text have been included in the list, and would be better omitted.

Companion to Manuals of Practical Anatomy. By E. B. JAMIESON, M.D. Sixth Edition. Pp. 736. London: Oxford University Press. 1945. Price 16s. net.

In this edition there are no important changes from the fifth, which appeared three years ago. For the anatomy student it will continue to be a most valuable book, for it is literally a handbook which can conveniently be carried in the pocket; yet it is a very clear and adequately complete text-book on anatomy, though it is rightly titled a "Companion," for there are no illustrations and it is written for use in association with the practical manuals.

BOOKS RECEIVED

BISPHAM, WILLIAM N.	Malaria: Its Diagnosis, Treatment and Prophylaxis. (*Baillière, Tindall & Cox, London*)	19s. 6d.
HERZBERG, ALEXANDER, M.D., PH.D.	Active Psychotherapy. (*William Heinemann (Medical Books) Ltd., London*)	12s. 6d. net.
JONES, D. W. CARMALT.	Annals of the University of Otago Medical School, 1875-1939 (*A. H. and A. W. Reed, Wellington, New Zealand*)	—
KERSLEY, G. D., M.A., M.D., F.R.C.P.	Outlines of Physical Methods in Medicine (*William Heinemann (Medical Books) Ltd., London*)	6s. net.
OLMSTED, J. M. D.	Francois Magendie (*Schuman's, New York, U.S.A.*)	$5
WILSON, C. W., M.SC., PH.D., F.INST.P.	Radium Therapy, Its Physical Aspects. (*Chapman & Hall Ltd., London*)	18s. net.

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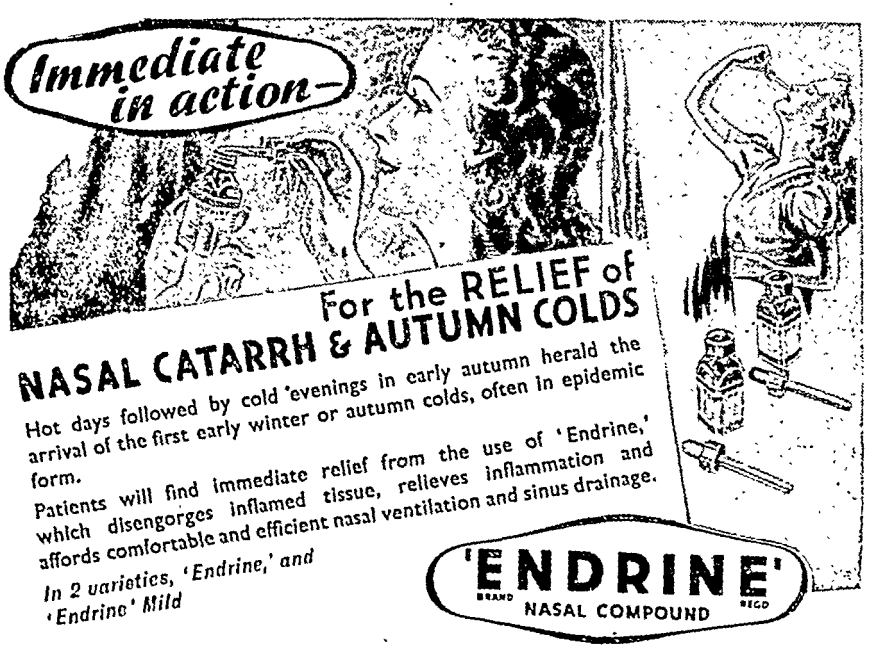

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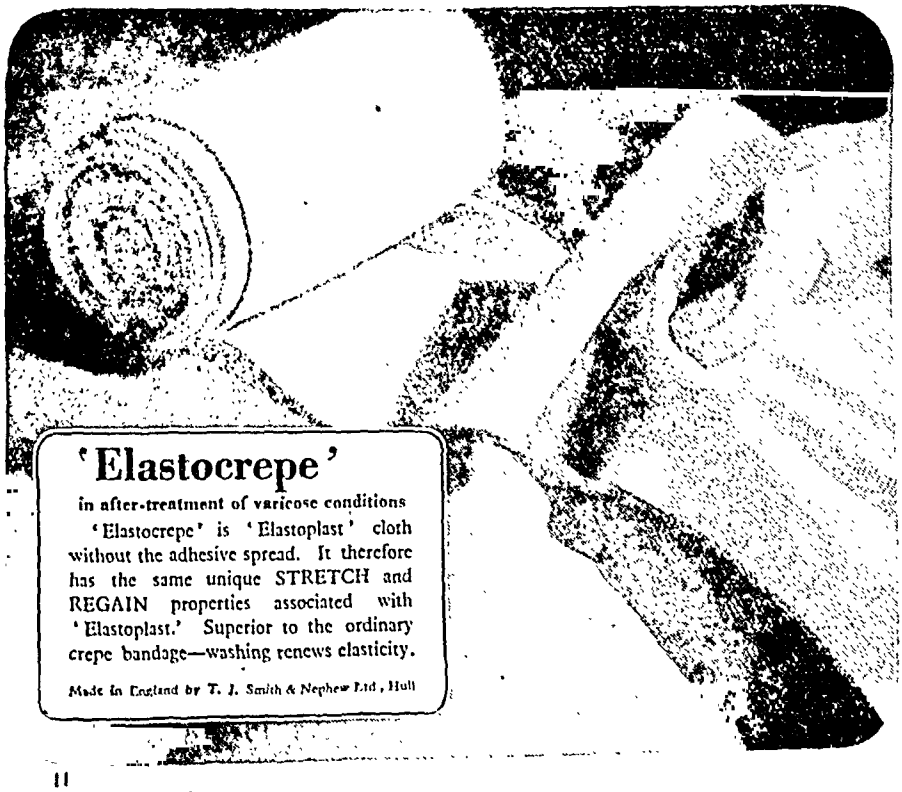

Edinburgh Medical Journal

September 1945

THE PHYSIOLOGY OF PERIPHERAL NERVE INJURY *

By ANTHONY E. RITCHIE, M.A., B.Sc., M.B., CH.B.

From the Department of Physiology, University of Edinburgh; and Gogarburn Peripheral Nerve Unit, Scottish E.M.S. Hospitals

INTRODUCTION

THE diagnosis of peripheral nerve injury is primarily anatomical. As the definitive treatment is in the first instance surgical, requiring precise location of the site of the nerve damage, detailed knowledge of the motor and sensory distribution of the peripheral nerves is the main instrument of the clinic. But the functional alteration in the various tissues described as "paralysis" or "sensory loss" is of

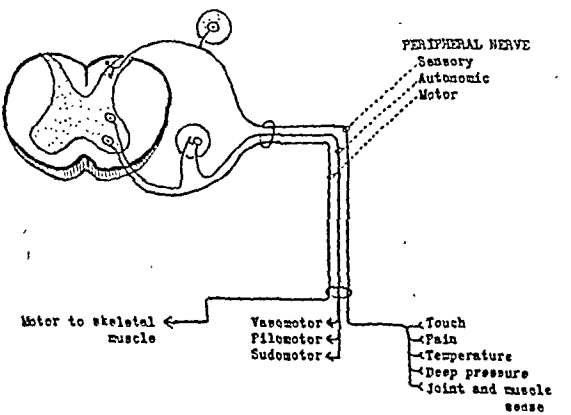

FIG. 1.—The main physiological components of peripheral nerve.

interest to the physiologist, and can sometimes supply additional information to an anatomical account of a nerve lesion. From this point of view there are three major physiological components liable to damage in a nerve (Fig. 1). The sensory fibres convey the several modalities of sensation to the central nervous system; the lower motor neurones transmit the impulses controlling voluntary contraction and reflex tone in skeletal muscle; and the autonomic fibres

* A Honyman Gillespie Lecture delivered in the Royal Infirmary on 15th February 1945.

operate the musculature of blood vessels and hair follicles, and are secretory to the sweat glands of the skin. Anatomical observation of the regions and muscles altered in activity can give a fairly exact definition to the level at which nerve interruption has occurred.

There are three main types of injury which are commonly encountered in war-time surgery (Seddon, 1943), and each presents different problems of diagnosis and prognosis. In the first place we have the relatively mild degree of axon injury (Fig. 2) which abolishes or impairs impulse propagation over a length of the fibre but leaves the end-organ attached to an intact and normal axon; these are the "pressure palsies" which recover spontaneously after removal of their cause. Secondly, we encounter the class of nerve damage named "axonotmesis" by Seddon, wherein the axon itself is so severely damaged as to undergo Wallerian degeneration distal to the injury; such lesions occur in general after severe pressure, contusion, or toxic

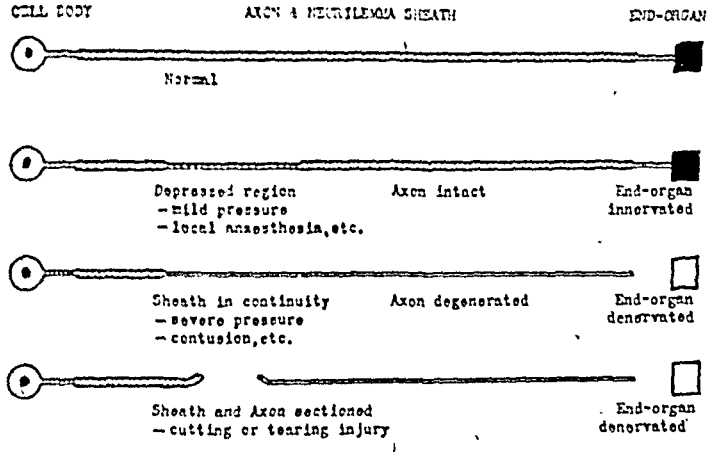

FIG. 2.—Scheme of the three physiological types of peripheral nerve injury.

applications, and leave the neurilemma tube and supporting connective tissue intact and in continuity so that the regenerating axon tips can grow down the tubes which they originally occupied. Thirdly, the nerve may be so severely injured that it is completely severed through axons and supporting tissues together, and these are the injuries which require surgical apposition of the cut ends in order that new axon tips may have the best possible chance of entering the peripheral stump. In the lesion of complete section with anatomical separation the pattern or arrangement of the neurones is essentially destroyed, for a regenerating axon approaches and enters at random a peripheral neurilemma tube which may or may not lead it to the right sort of end-organ, and at the best can hardly be expected to conduct it to the identical end-organ which it innervated before the wound was inflicted. The histological picture of regeneration and its practical significance has been very beautifully worked out by Young and his colleagues. (Young, 1942.)

Although these latter two types of nerve injury—axon section

and complete nerve section—bear such widely different prognosis as regards ultimate result, it is important to realise that they cannot be differentiated from an examination of the region of sensory loss or of the paralysed muscles, for once degeneration has occurred the end-organs are denervated in both instances. Short of exploratory operation only the rapidity and extent of recovery indicate axon section as opposed to nerve section with its accompanying axon shuffling. It is in respect of early detection of recovery that physiological investigation has its part to play, and this lecture deals mainly with an outline of the methods used in the assessment of denervation and regeneration of peripheral nerves in man.

Autonomic Denervation

Section of the autonomic fibres in a peripheral nerve results in the familiar clinical picture of loss of vasomotor control, absence of spontaneous sweating, and abolition of the " goose-flesh " or pilomotor reaction in the area supplied by the fibres. The area which a given nerve supplies with autonomic fibres is a relatively small one, and there appears to be a very extensive overlapping of such fibres in their peripheral distribution, which, moreover, is extremely variable from one individual to another. The area in which autonomic denervation can be detected is usually similar to but rather smaller and more inconstant than that in which sensory changes result from section of the nerve. (List and Peet, 1938 ; Guttmann, 1940 ; Richards, 1943.)

Static Tests of Denervation.—The first characteristic feature from the physiological point of view is the absence of spontaneous activity mediated through central nervous system pathways. This results in the basal state of the denervated area being affected as regards its skin temperature, sweating and pilomotor activity, and this functional depression can be detected and measured by what may be described as static tests. Skin temperature is best measured by means of a small bimetallic thermocouple connected to a galvanometer at a convenient distance, and under ordinary circumstances an area of lower temperature represents the region of vasomotor denervation. Plethysmographic methods can be adapted to measure the reduced blood flow ; though their use is less convenient in the clinic and their results liable to be rendered difficult of interpretation because of the blood flow in the deeper tissues (Barcroft, Bonnar, Edholm and Effron, 1943). Absence of sweat gland activity can be demonstrated in various ways, of which two are in general use. The application to the skin of some chemical which develops colour in the presence of moisture affords a visible impression of the inactive area ; iodine-starch mixture (Minor, 1928) or a dye known as chinizarin (Guttmann, 1940) both turn a deep blue colour over parts of the limb which are normally sweating, but remain colourless over denervated areas so that a photographic record may readily be made of the precise region. An

alternative method, more exact but more laborious, is to measure the resistance which the skin offers to the passage of an electric current; skin resistance is very largely altered by presence of sweat, and the denervated area can be plotted as one of high resistance with a sharp line of demarcation separating it from surrounding normal skin (Richter and Woodruff, 1941; Shumacher, 1942). Pilomotor loss is not so readily tested, but if the subject is exposed to cold, or suddenly placed in a hot bath, waves of "goose-flesh" can be seen passing over the limbs but avoiding the denervated territory.

Reflex Tests Over Central Pathways.—In addition to these static tests of basal level there are a large number of true physiological tests which are active ones in the sense that the reflex mechanism is artificially provoked and the presence or absence of the response noted as a resultant activity. These reflex tests are operative at different levels of the nervous system. One of the most effective tests of autonomic integrity is that known as the reflex vasodilatation test, in which immersion of any part of the body (conveniently the extremities) in hot water produces after a short time a reflex opening-up of blood vessels in the other extremities as recorded by skin temperature or plethysmographic methods. In this way the response of an area, and not merely its basal level, can be estimated; the denervated region which no longer has its efferent pathways does not respond, and stands out in contrast with its normal surroundings. A similar test uses sudomotor activity as its indicator; the rapid alteration of skin resistance in response to sensory stimuli has been popularised as the so-called "lie-detector" on the somewhat unfounded assumption that an individual's nervous activity on telling a lie exceeds that on telling the truth, a principle which unjustly favours the practised sinner. This particular response can be so precisely measured that it has recently been used to determine the velocity of sympathetic nerve fibre transmission in man (Carmichael, Honeyman, Kolb and Stewart, 1941). The "cold pressor" test, first described by Hines and Brown (1932), is yet another example of reflex autonomic activity shown as a transient rise in blood pressure from increase of peripheral vascular resistance following on short exposure of the hand to cold. These reflexes all involve central pathways of some complexity, and their efferent pathways comprise both pre- and post-ganglionic autonomic neurones. In so far as they are dependent also on the integrity of the sensory side of the reflex arc as well as upon the motor, they can be used with minor modifications for other indications; for example, the cold pressor response not only requires an active vasomotor constriction to raise the blood pressure, but also has to have an intact sensory pathway from the cold limb to the central nervous system. As applied to peripheral nerve injury examination, they are used as indicators of the integrity of the post-ganglionic fibres, although they are also abolished by section of pre-ganglionic fibres or by damage to their sensory afferent connections.

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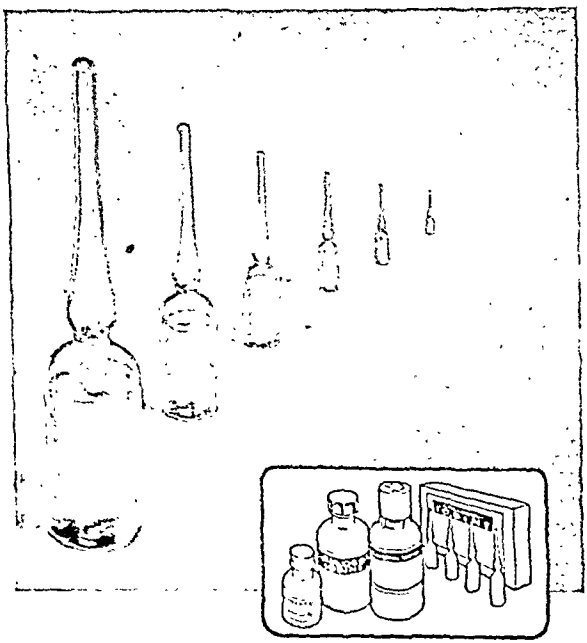

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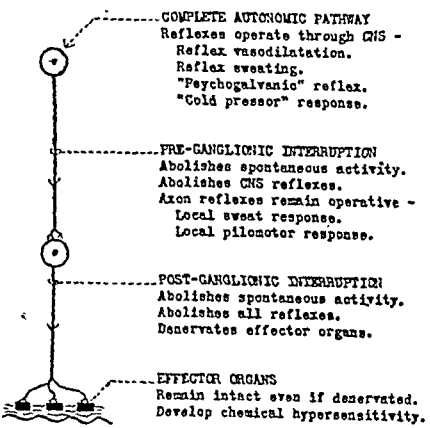


FIG. 3.—Scheme of levels of autonomic skin reflexes.

sympathetic plexus in the skin, and is therefore a true axon reflex involving antidromic propagation of nerve impulses over part of the network (Lewis and Marvin, 1927; Wilkins, Newman and Doupe, 1938). It is not dependent on pre-ganglionic pathways or on sensory afferents, but disappears when the post-ganglionic fibres are cut and have had time to degenerate. These local reflexes are therefore a strict test for post-ganglionic integrity.

Effector Organ Sensitivity.—At a yet lower level of complexity we have to consider the function of the terminal effector organs when they are totally denervated, as they are in the post-ganglionic section which peripheral nerve injuries usually involve. The denervated effector organ—plain muscle of blood vessel or hair follicle, or sweat gland—does not itself degenerate, but remains in a potentially useful condition for an indefinite time if its nutrition is unimpaired. Completely severed from its nerve supply it cannot be operated by any reflex pathway, but can be rendered active by chemical substances released in its neighbourhood. Not only does this chemical sensitivity

persist, but it is usually increased very considerably so that small amounts of appropriate substances circulating in the blood stream may produce greatly exaggerated effects in the denervated region. This chemical sensitisation has been described by Cannon (1939) as a general "law of denervation," and applies not only to autonomic effector organs but also to ganglion cells and to voluntary muscle fibres. From the practical aspect it presents the surgeon with a problem; post-ganglionic autonomic section will abolish spontaneous activity of effector organs, but by denervation will sensitise them to blood stream agents. The excessive response of denervated arterioles to adrenalin and of sweat glands to minute amounts of acetyl choline in the blood makes it necessary for the surgeon to carry out a nerve section which abolishes spontaneous activity, but does not denervate the effector organs—namely, a pre-ganglionic section—when the operation is carried out for therapeutic purposes. In the case of peripheral nerve injury the autonomic section is a post-ganglionic one, and for a period vasoconstrictor tone is removed from the blood vessels, the sweat glands are inactive and goose-flesh no longer appears. But after a variable period of time, usually a few weeks, the effector organs recover a considerable power of response to local conditions. The calibre of the blood vessels becomes dependent on their immediate environment, and in this climate they tend to remain constricted, with the result that the denervated part enters on a cold phase which will normally persist until re-innervation takes place. But that the vessels retain their powers of altering their size in response to local conditions can be seen in the fact that a denervated digit which has become infected may show a temperature greater than that of the surrounding normal skin because of the vessel's reaction to locally produced metabolites.

Sensory Denervation

Division of the sensory components in a mixed nerve produces clinical manifestations which are well known, but whose physiological basis is still a subject for conjecture and experiment. In the simplest descriptive terms the resulting region of sensory loss consists of an area wherein light touch, as with cotton wool, is not appreciated, and a somewhat smaller inner area where the sensation of pin-prick is absent. As in the case of autonomic distribution, there is a considerable overlap between adjacent sensory nerve territories and individual variation is common.

Many attempts have been made to interpret these findings in terms of anatomical fibre arrangement and physiological activity. The description of Rivers and Head (1908) remains as the clinical standard of observation, although the well-known theory of "protopathic" and "epicritic" sensory mechanisms (Head, 1920) is inadmissible in the light of modern neurophysiology. Walshe (1942),

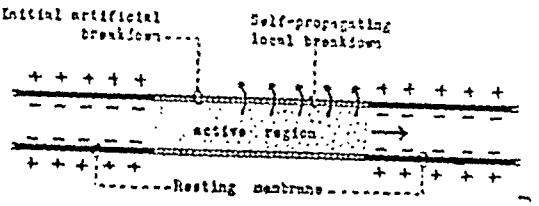
in a critical review of the anatomy and physiology of sensibility, stresses the view that sensation depends on two factors: the anatomical overlap and distribution of the terminal nerve endings to a "sensory unit" of some size, including several individual end-organs, and the known existence in the sensory nerve of several components having different threshold values for excitation and different conduction rates. In so far as this attitude depends on data which have been directly verified and requires no other postulate, it is a very attractive one, and has recently been given some further experimental support by Bishop (1944), employing a new technique for the excitation of single skin sensory organs in man. There are many who feel, nevertheless, that it does not adequately explain certain clinical findings. Lewis (1942) believes that a dual mechanism does, in fact, exist in the skin to subserve sensation, but that one part of it—the "Nocifensor" system—is not directly afferent to the central nervous system, but is concerned with a local chemical release arrangement. Reference must be made to these authors themselves, as space does not permit more than the mention in the bibliography of this paper of some of the recent works on the subject. Because the response to sensory stimulation is perceptive, and not readily assessed by quantitative methods, neurophysiology has had less to contribute to the clinic in this field than in other aspects of nerve injury, and the cotton wool and the pin remain the instruments of choice. Until we have a practicable method of observing and identifying the action potentials in the intact sensory nerves a great deal must be left to conjecture. Rusinov (1943) has reported the successful recording of sensory activity in a main nerve in man, and claims to have identified the impulses subserving pain, but the observation awaits confirmation. There is little doubt that the possibility will be realised with the rapid growth of technique, and we shall then be in a position to review the story with an active physiological background.

Motor Denervation

The physiological effects of section of motor nerve fibres provide the opportunity of studying many of the features of the classical nerve-muscle preparation as they occur in man. On interruption of the lower motor neurones immediate flaccid paralysis ensues in the muscles supplied by them, and the straightforward clinical investigation of motor defect consists of identifying the individual muscles which are no longer working. In any particular patient this may, or may not be an easy task, as trick movements carried out by muscles other than the normal rapidly develop in some persons, and anomalous innervation of muscles, especially in the hand, is more common than formal anatomy would have us expect (M.R.C. War Memo. No. 7, 1943). Since the middle of the nineteenth century artificial stimulation of muscles has been used in the testing of nerve injuries, and information

is often expected which the physiological limitations of the method cannot allow. One of the aspects of nerve injury work which has been important during the last few years has been to establish the maximum help that the clinic can expect to get from the dramatic and attractive process of artificial excitation, and to devise means whereby that information can be obtained as simply as possible. It is of value to review briefly the present state of knowledge regarding the excitation of tissues by electric current.

The Excitation and Propagation of the Nerve Impulse.—We have not hitherto been considering the excitation of the nerve impulse in the neuron at sites other than its normal inception, namely the spinal cord motor cell bodies or the sensory termination, as the case may be. But from the study of the excitability of the axon itself neurophysiology has created a picture of the activity of nerve which has been gradually



The polarised membrane conception of axon activity.

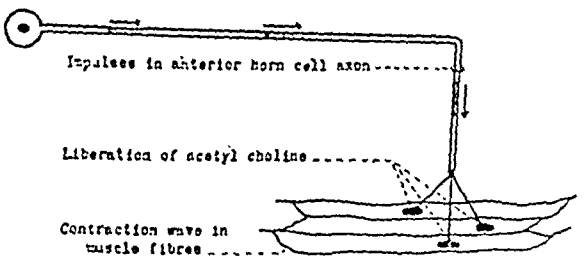


FIG. 4.—Diagram of the motor unit and transmission from nerve to muscle fibre.

extended to a fundamental concept of all nervous activity (Gasser, 1939). During the last few years that concept has had several important additions and clarifications, and although they are not immediately concerned with peripheral nerve injury as such, they are of vital importance in understanding nervous activity.

The axon, or axis cylinder, is to be regarded as surrounded by a bounding membrane which is permeable to some ions, but not to all (Fig. 4); in the static state when no impulses are being propagated this cylindrical membrane becomes polarised by reason of differential accumulation of ions on either side; that is to say that a potential difference develops across the membrane and is maintained continually by the selective permeability of the membrane. On localised destruction or impairment of the membrane (for reasons of convenience and accuracy an externally applied electric current is used), the barrier separating the charged ions is caused to leak; the resultant neutralisation of the charges is necessarily accompanied by a local flow of current

through the no longer impermeable membrane. If the initial breakdown is sufficiently extensive or complete, this local current appears to be of such a strength and distribution as to cause annihilation of the intact membrane immediately adjacent, which results in a further local current of the same nature, only a little farther along the membrane tube. Once started under suitable conditions this process is self-propagating, so that a wave of membrane instability accompanied by neutralisation of its charges passes along the axon until it reaches the termination. If the artificial stimulation is applied to a point in a length of axon, there is obviously nothing in the axon structure to determine the direction in which the wave will travel, and in fact, as might be expected, it will travel in both directions away from the point of stimulation—this has been omitted from Fig. 4 for simplicity. In the intact neurone impulses are initiated only at the appropriate end, and this complication does not arise. It is this wave which is described as the nerve impulse and which can be detected as a brief potential change—the action potential—by a sensitive instrument placed on or near the surface of the nerve. When the nerve impulse arrives at the end-organ, and we shall consider in the first instance the termination of the motor nerve fibre as the end-plate in skeletal muscle, it is generally agreed that the substance acetyl choline is released at the neuro-muscular junction; this chemical in turn causes depolarisation of the muscle fibre, which initiates a propagated wave in the fibre, this time accompanied by a wave of active contraction. It was suggested many years ago that there was a close physiological analogy between the skeletal muscle fibre and the post-ganglionic neurone, and more recent work has strengthened this resemblance. In both cases the chemical agent acetyl choline is interposed between two impulse-conducting structures; in both cases a single primary fibre has access to a considerable number of muscle fibres or post-ganglionic axons as the case may be; and the pharmacology of the autonomic synapse corresponds very closely to that of the neuro-muscular junction. The comparison is, of course, quite illegitimate morphologically, but is a convenient one for physiological consideration.

Superimposed on this very brief outline there is a keen controversy with regard to the fundamental operation of nervous tissue, particularly in the central nervous system. One school of thought has maintained that synaptic transmission in the central nervous system is an electrical phenomenon involving the action potential, which is held to arrive at the synapse and excite across it in a way exactly comparable to the arrival of an artificial electric stimulus. The opposing school has pointed out that, as a chemical transmitter has been well established as a fact in peripheral mechanisms, it is to say the least of it unlikely that an entirely different mechanism operates over the histologically similar central synapses. Opposition to the chemical theory has largely been based on the very short intervals of time which are measured as synaptic delay, and which would involve the extremely rapid synthesis

and breakdown of the chemical transmitter in the central synapses. Within the last two or three years new discoveries have revealed a common ground for mutual agreement of these views. Nachmansohn (1941) and his colleagues have recently reported that acetyl choline is not only a product of the synapse or neuromuscular junction, but appears to be an essential constituent of the axon itself. It has further been estimated that the requisite amounts of acetyl choline to excite across synapse or neuro-muscular junction can be synthesised (Feldberg, 1943) and broken down in the short time available for the process (Nachmansohn, 1939). These findings await application to certain of the more obscure and inaccessible problems of central transmission, but allow us to consider the axon mechanism and the transmission between axons in the same terms. Boell and Nachmansohn (1940) have shown that the specific enzyme for breakdown of acetyl choline is located in the boundary or sheath region of the axon, and is not present in any quantity in the central axoplasm; Fulton and Nachmansohn (1943) suggest that the nerve impulse itself is dependent on the synthesis and breakdown of acetyl choline in or near the sheath of the axon, and that its appearance in easily recognisable quantities at the autonomic synapses and neuromuscular junctions follows as a consequence of the greater surface offered by the arborisation for its liberation. The evidence is strongly in favour of the fact that acetyl choline is a primary factor in the transmission of nerve activity both in the axon and across the junctions. The most conclusive proof that acetyl choline is in fact the axonic transmitter as well as the synaptic still leaves us with the breakdown of the polarised membrane to explain in terms of acetyl choline effect on permeability, for the account given of impulse propagation remains unaffected. There is no doubt that during the passage of the nerve impulse the permeability of the axon membrane decreases, and is rapidly restored in the refractory period of the fibre, and the identification of a specific chemical apparently concerned with this change is a basic advance in our understanding of nervous mechanisms.

The Excitability of Nerve and Muscle.—The excitability of nerve or muscle can be expressed in terms of the stimulus necessary to depolarise or break down the barrier membrane for a sufficient time or distance to initiate the self-propagating wave. It can be deduced from theoretical reasoning, and confirmed experimentally, that the time for which the artificial stimulus is applied is as important a factor in this initiation as its intensity. A certain minimal strength of stimulus is called for, and this threshold intensity must persist for some considerable time before producing an adequate effect on the polarised membrane. Any stimulus which lasts for a shorter time must be of accordingly greater intensity, and at the other extreme of the scale we can apply a stimulus of such brief duration that a very high intensity will be required to produce response. This range of stimulus values is known as the " intensity-time " relationship for threshold stimuli,

and is a rigid quantitative measure of the excitability of any tissue. Two points on the curve expressing the relationship (Fig. 5) are specified by title; the long-lasting minimal-strength stimulus is called the rheobase, and another point has been given the name of chronaxie, and defined as that duration of stimulus twice rheobasic strength which is the shortest necessary to bring about excitation. It will be noted that the chronaxie is an arbitrarily selected point, that it is specified in units of time, and that it does not imply any definite value of rheobase.

The classical testing of muscle by means of the galvanic and faradic currents can be quite simply related to this curve of intensity and duration. Galvanic shocks last for a relatively long time and are of low intensity; faradic currents are brief but relatively intense, and therefore apply to a region of the curve where the threshold intensity is elevated. Neither galvanic nor faradic current can readily be

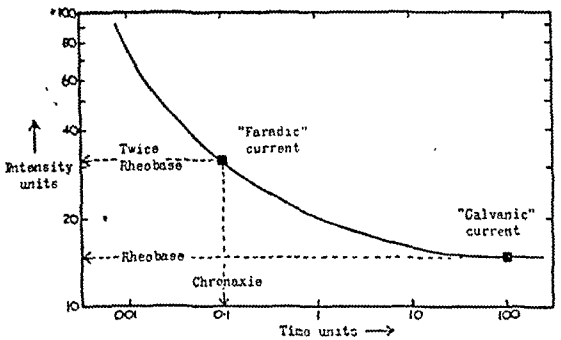


FIG. 5.—The Intensity-Time relationship of threshold electrical stimuli for any excitable tissue. Rheobase is defined as the minimum intensity of indefinite duration; chronaxie as the duration necessary for a stimulus of twice rheobasic value.

Faradic shocks are of short duration and relatively high intensity, galvanic shocks of long duration: neither are commonly estimated quantitatively.

measured in ordinary muscle testing, and it is not usual to give actual values. It is ordinarily taught that whereas normal muscle is excitable by both galvanic and faradic current, denervated muscle responds only to galvanic stimuli because the faradic shock is too brief. This is only partly true, because the fact that denervated muscle will not respond to the faradic current as ordinarily applied is largely a reflection on the low intensity of the average coil; it is not difficult to demonstrate (with a large coil and a reputation for inhumanity) that faradic current, if strong enough, will stimulate denervated muscle. At the same time, the assessment of muscle denervation by absence of faradic response is a well-established and generally satisfactory procedure in practised hands. But modern electronic technique has made it possible to design reliable and simple stimulators for investigating the complete intensity-time curve of human muscles with little more trouble than is involved in the older test (Bauwens, 1941; Ritchie, 1944). One of the typical records is given in Fig. 6, which shows the quantitative

expression of the difference between the excitability of normal and of denervated muscle; a single curve is not given for each type, but the composite ranges for the mean values taken from a series of 50 cases have been plotted on the same scale. It can be seen that only the very shortest stimuli require an intensity increase in the case of normal muscle, whereas denervated muscle demands a steady and considerable increase in voltage as the duration of the stimulus is decreased. Such records afford us in the first place a reliable and quantitative method of identifying denervated muscles by their thresholds to electric shocks. Intensity-time curves of muscle excitability also afford an early indication of regeneration; records taken carefully at weekly intervals show an increase of excitability in re-innervating muscle a short time before voluntary activity can be detected in the muscle by clinical means. In high nerve injuries this increase of excitability as indicated by the intensity-time curve is the earliest sign of re-innervation (Ritchie,

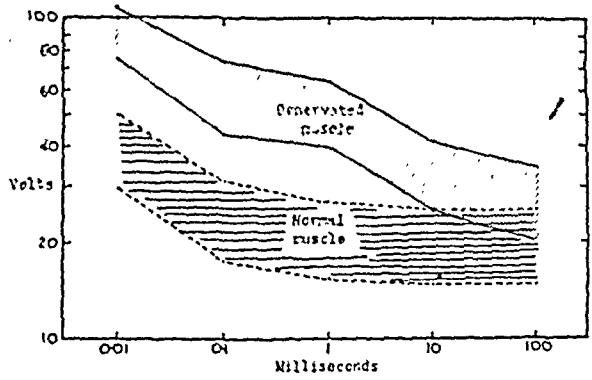


FIG. 6.—The Voltage-Time curves for normal and for denervated muscle. Mean value plus and minus Standard Deviation of 50 cases of known denervation; normal contralateral muscles as controls.

Figures taken from various muscles of forearm and hand.

1945). The method has, nevertheless, very definite limitations; it is of no help in distinguishing directly between the axon lesion in continuity and complete nerve section, and it gives no account of the amount of power which the muscle will ultimately recover.

The Property of "Accommodation" in Muscle.—There is a second physiological principle of excitation which can usefully be employed in the assessment of denervation in human muscle. One of the characteristic features of excitable tissues is their capacity for adaptation or accommodation to a stimulus which is applied gradually over a relatively long period of time. We have so far been considering stimuli which rose to their threshold value almost instantaneously, and we have shown that the effectiveness of such is compounded by their intensity and their duration. But the suddenness with which a stimulus is applied is a further factor which greatly modifies its efficiency as a depolarising agent. A tissue which has a particular threshold value for an instantaneously applied stimulus will not respond at that value if the stimulus is so arranged as to reach that

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value gradually. This property of giving before a gradual stimulus, of resisting depolarisation if given time to do so, is referred to as "accommodation" in muscle, and is variable in degree. The same phenomenon is observed in sense organs, where it is described as "adaptation." Accommodation is accounted for by the properties of the polarised membrane, which, as we have seen, tends to restore itself to a resting state after any impairment of its selective permeability. If the forces tending to depolarise act gradually, the membrane will have a chance of partially restoring the normal polarisation; if the forces act very gradually, adequate depolarisation to initiate propagation may never come about, with the result that, despite a very high ultimate value of stimulus, response is absent.

Accommodation in human muscles can be measured by various methods (Solandt, 1935; Pollock, Golseth, *et al.*, 1944), and in this respect again we find a marked difference between the properties of

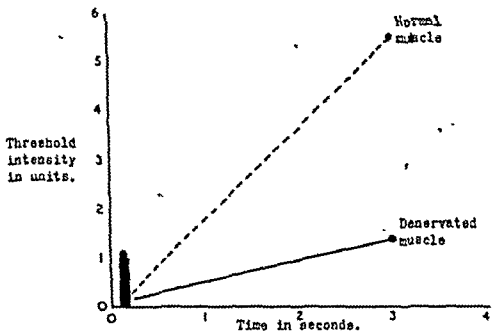

FIG. 7.—Stimulus "accommodation" in normal and denervated muscle. Threshold to instantaneous stimulus = 1 unit of voltage. Stimulus applied gradually rising for three seconds:—Normal muscle raises threshold 5·5 times. Denervated muscle raises threshold only 1·4 times. Mean figures from 14 cases.

normal and of denervated muscle. Normal muscle possesses the power of accommodation in a considerable degree (Fig. 7), and a current which rises gradually for three seconds must reach a value nearly six times that necessary for an instantaneous current to produce response. Denervated muscle, on the other hand, behaves as a tissue with very little power of accommodation, and in such muscle the three-second rising current will excite at an ultimate value only 1·4 times the threshold to instantaneous application. This type of stimulation has recently been applied to the study of denervation in nerve injury cases by Pollock; in general it is not quite so convenient for diagnostic use as the intensity-time curve technique, and there is no evidence that it supplies additional information. For therapeutic purposes, however, the use of slowly rising and falling currents has an important application. There appears to be little doubt that, in man, it is advantageous to administer regular electrical stimulation to denervated muscles during the period that elapses between injury and re-innervation. Adequate stimulation does have a part to play

in the maintenance of the size and nutrition of the inactive muscles until regeneration of the nerve supply permits of active voluntary exercise. A slowly rising and falling current, such as alternating current of 0·2 to 1 cycle per second, can bring about contraction in denervated muscle without setting up response in surrounding normal muscles whose accommodative processes are sufficiently rapid to evade stimulation by such slowly altering currents. As one of the difficulties in artificial exercising of denervated muscle is the violent contraction that galvanic current applications often set up in the normal muscles of the part, causing wrenching of the weak muscles and discomfort to the patient, the use of these slowly varying currents in treatment is an important one. A comparative clinical trial of the effects of galvanic exercising as usually carried out compared with stimulation by low-frequency alternating currents in respect of their ability to maintain bulk and nutrition of paralysed muscle would be a valuable contribution to physio-therapy.

The Recording of Muscle Action Potentials in Man—the Electromyogram.—In conclusion, there is another and totally different method of examining the activity of the peripheral motor mechanism in man, which depends on the detection and identification of muscle cell activity as revealed in its action potentials. The anatomical muscle is organised on the basis of functional units, each one composed of a group of 100-150 individual fibres activated synchronously by a single motor nerve axon (Denny-Brown and Pennybacker, 1938). The electrical potentials which represent the spread of the contraction wave in such a motor unit are small and transient, and only recently has the apparatus for their recording become practicable outside the laboratory. The modern development of the cathode-ray oscillograph into a robust and foolproof piece of apparatus has given us an indicator whose pointer—the electron beam—is inertia-free and unbreakable; but the cathode-ray tube is itself a very insensitive device, and its physiological use has depended on the technical improvements in valve amplifying gear whereby the action potentials can be magnified hundreds of thousands of times with complete fidelity before visual presentation on the screen of the tube (Parr and Walter, 1943). Electrodes placed on the surface of the muscle have been used, but tend to give a confused picture of the underlying activity, and the collection of the action potentials is usually done with a concentric needle electrode (Adrian and Bronk, 1929) which has a very fine insulated wire down the lumen and can be inserted into the muscle bulk with trifling discomfort, and remain in position while the potential changes are observed on the cathode-ray tube and loud-speaker (fig. 8). It is not practicable to construct a needle electrode which can be inserted into a single muscle fibre in man, but it is possible to make one comparable in size of tip with the motor unit group of fibres which normally act as one, and roughly correspond with the fine muscle fasciculi (Wohlfart, 1937).

When full voluntary contraction in a healthy muscle takes place, the record of action potentials from the muscle fibres is considerably confused (Fig. 8), because not only is the motor unit nearest to the needle tip active, but also many similar units round about, and the resultant changes consist of a very irregular row of asynchronous spikes of varying amplitude. In weak voluntary contraction the motor units contract less frequently, and because fewer are in action the trace is not so confused by surrounding activity, and the waves resulting from one or two motor units may be clearly seen and heard, and their rhythm identified. In complete voluntary relaxation no action potentials may be detected; more commonly the subject cannot achieve complete absence of muscular tension, and the residual muscle tone shows up as the appearance of motor unit spikes at a slow regular rate.

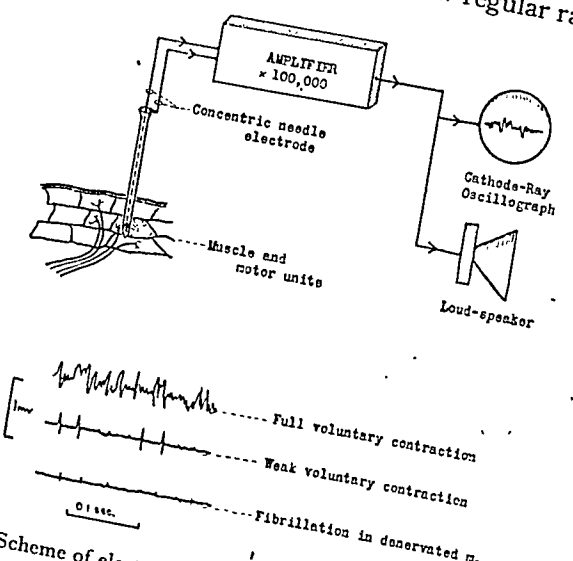

FIG. 8.—Scheme of electromyogram for recording muscle potentials.

The record from denervated muscle is quite different. In motor units whose nerve supply has degenerated no normal action potentials can be found, and instead a number of very small and irregular spikes appear on the screen arising from the random contraction of individual muscle fibres, probably from chemical or mechanical irritation. These are known as fibrillation potentials and persist throughout the period of denervation unless complete fibrosis of the muscle elements sets in; as re-innervation of the muscle proceeds, the fibrillation potentials are replaced by the normal action potentials indicative of motor unit function. Normal action potentials can be detected a short time before voluntary power is found in a re-innervating muscle, but in this respect the electromyogram needle has a drawback inseparable from its small size—it

may or may not record from an active motor unit in a bulky muscle wherein both normal and denervated muscle fibres co-exist. As the re-innervation of a muscle proceeds at random as regards distribution of completed units, a single needling may indicate denervation by the demonstration of fibrillation potentials, although in some part of the muscle relatively remote from the needle tip newly innervated units may in fact exist and require several needlings for their identification. A series of observations of this type on patients suffering from peripheral nerve injury has been presented by Weddell, Feinstein and Pattle (1944).

In conclusion, I have been concerned in this lecture in outlining applications of relatively simple physiological techniques to one particular problem of human injury; not because such methods have been of dramatic or startling value to the clinic, but rather with the idea of demonstrating that physiological princples are not restricted to the laboratory and can be applied with advantage to the most interesting experimental animal—the human. There are a great many such applications of physiology awaiting trial; even in this field I have only referred to a few out of the many which are used and the vast number which are possible. As adjuncts to the clinic they are directly useful to a certain extent; but their real value lies in the steady flow of new information which they supply, perhaps slowly, regarding the function of living tissues in the human subject. This understanding of activity is the foundation of advance in every branch of biological science. There is a further justification in being concerned with the technique and methods of neurophysiology as applied to man. During war-time instruments and methods are devised by physicists and engineers under pressure of urgency which develops their use at a rate far exceeding that of normal times. New inventions, and old ones developed to routine practicability, will be handed over in the next few years to the biologist for adaptation and application. Many of these will play a part in advancing the work of the laboratory and of the clinic, and this is especially true of neurophysiology. A review of this subject in five years' time will present a far clearer picture of the activity of the nervous system in man than can be given at present. I have been concerned with an account of some of our work just now in this field of applied physiology; it must serve merely as an introduction to the advances, firstly technical, then in the laboratory, and finally in practical medicine, that the next few years are going to bring forth.

The privilege of delivering this lecture is due not to myself as an individual, but as the spokesman, on this occasion, for a team concerned with the problems of the peripheral nerve injuries that occur in the course of war. I therefore wish to express my thanks to the staff of the Gogarburn Unit, and in particular to Professor J. R. Learmonth and Dr R. L. Richards, from whom I have borrowed much material and received every assistance. I am additionally indebted to Professor I. de B. Daly for advice regarding the preparation and presentation of the material.

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SHOCK DUE TO TISSUE TRAUMA

OBSERVATIONS ON DIAGNOSIS AND ASSESSMENT

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AT present the most important clinical task in the "shock problem" seems to be to ensure that shock is recognised at such an early stage as to allow the timely application of the efficient therapeutic methods now available. Shock of varying severity is a frequent accompaniment of severe injuries and of many of the extensive operations which technical advances in surgery and anæsthesia now render possible. Sometimes it is ignored until a critical stage has been reached.

Information obtained from animal experiments is of limited value, and there appeared to be scope for more direct clinical study of the shocked patient in the hope that thereby standards might be established by which the patient's condition could be judged. More than 100 patients, suffering from the effects of severe injury or extensive surgical operations, have been studied, 43 of whom were observed in detail at the bedside and in the operating theatre for many hours. In this series the term "shock" applies to the circulatory failure which is found within a few hours of severe injury as the result of factors other than gross infection or asphyxia. Strictly speaking, shock should be diagnosed only when there has been initiated that series of changes which, unbroken by treatment, will lead to death. Often in the present investigation this condition was satisfied in many cases, as many patients died.

CLINICAL APPEARANCES

O'Shaughnessy and Slome (1935) suggested that the difficulty in defining the term "shock" could be overcome by providing instead an accurate clinical picture of the syndrome. A single picture is inadequate, since frequently the appearance of shocked patients differs from the classical description of a pallid, apathetic individual with a cold, clammy and perhaps slightly cyanosed skin, lying quietly on his bed or stretcher with little or no interest in his surroundings, shivering from time to time and complaining of intense thirst. Three other types of response which have been observed are described below; that associated with the severe form of neurogenic shock following serious head injury is not included.

(1) At first some patients appear to be little affected by severe injury, they are quiet but not apathetic, their skin is warm and red and they may complain of feeling too hot after having been put to bed, but pain is seldom mentioned and the blood pressure is not

markedly depressed until an hour or two later when it may have fallen to a very low level and the signs of established shock are present.

(2) From the time of injury other patients talk volubly, giving advice to their attendants in a loud and confident voice and describing their accident with a wealth of circumstantial and often irrelevant detail. They may be pale but usually do not sweat, are not chilled and do not complain of pain. Their injuries are severe and the blood pressure is low.

(3) After very extensive burns or multiple limb injuries, but in the absence of head injuries, there may be extreme restlessness which may be so marked as to be maniacal and require forcible restraint; it is little affected by ordinary doses of sedatives. Speech is slurred, thought is slow and irrational and the patient makes unreasonable demands and attempts to leave his bed, throwing off shock cage, bedclothes and restraining hands in spite of the most severe injuries. He then sinks into an uneasy doze from which he awakens after a short interval to repeat the same performance. Examination is extremely difficult as the slightest disturbance raises a storm of protest and resistance. Shivering is marked, the skin is pale, cyanosed and cold, the blood pressure is usually too low to be estimated, and many of these patients soon die.

Blood Pressure Changes

The blood pressure was repeatedly estimated in all patients of this series at intervals of from a few minutes to several hours, depending on the rate at which changes were taking place. While it is believed that such estimations are essential for accurate assessment, their frequency must be limited in view of the disturbance they cause to the patient, especially when observations are continued for many hours. The systolic level alone is of limited value, the diastolic and pulse pressures being also essential in forming a picture of the changes in blood volume and blood vessels. The systolic level was taken to be that at which sound was first heard and the diastolic level when the last sound faded. A mercurial sphygmanometer with a four inch inflatable cuff was used in all cases. From the results obtained the adult patients have been classified into four groups according to the blood pressure level; hypertension (systolic pressure above 140 mm. Hg.) normal (systolic pressure between 100 and 140 mm. Hg.) moderate hypotension (systolic pressure 60 to 100 mm. Hg.) and severe hypotension (systolic pressure below 60 mm. Hg.).

1. *Moderate Hypotension* (systolic pressure between 60 and 100 mm. Hg.) was found in the majority of patients studied, and with due regard to other factors, the severity of shock and its rate and direction of change were closely related to the alterations in the blood pressure levels. It has been repeatedly observed that shortly before a fall in systolic and diastolic pressure there may be a slight rise in both levels,

usually more marked in the case of systolic pressure. Such a rise was usually associated with a recurrence of blood or plasma loss during transfusion, or when the rate of a continued loss increased, apparently as the result of the transfusion. Alternatively there may be a small rise in diastolic pressure alone before the fall of both levels. When a fall in pressure occurred, the systolic level usually fell more rapidly than the diastolic, and the converse was equally true.

2. *Severe Hypotension* (systolic pressure below 60 mm. Hg.).—Of 10 patients of this type who were closely observed, the pressure in 7 was too low to be estimated at first. Severe hypotension may follow closely on serious injuries associated with considerable loss of blood or plasma, and has been observed particularly after gross crushing injuries of the upper thighs, two or more hours after very extensive burns or scalds and frequently after severe operations under general anæsthesia (such as excision of rectum or partial gastrectomy) in elderly and debilitated subjects. The diastolic pressure was often too low to be estimated, and in other cases the pulse pressure was only 10 to 20 mm. Hg. On a number of occasions the fourth Korotkov sound has remained audible until the cuff was empty. This has been associated as a rule with very severe shock and a systolic level below 60 mm. Hg., but also, though more rarely, with systolic pressures of over 120 mm. Hg. Provided that blood or plasma loss did not continue or recur and the injuries did not present insoluble problems, the blood pressure could be restored to a safe level by immediate and rapid transfusion of blood, plasma or gum saline, and maintained by continuation of the transfusion at an adequate rate. Without these measures such patients invariably died. Even when the systolic pressure had been below 60 mm. Hg. for as long as eight to ten hours, it was possible to overcome hypotension in a number of patients, though some died later from causes other than shock or the effects of transfusion.

3. *Hypertension* (systolic pressure above 140 mm. Hg.).—This was a comparatively rare type of response in the patients studied, being found on admission in only 5 out of 76 patients, but in 2 others, both young children, the pressure was between 130 and 140 mm. Hg. and these should be included. The elevation was usually confined to the systolic pressure, but in 2 cases there was also a significant diastolic rise. The radial pulse might be small or absent, in some instances it was hard but poorly sustained, and its character varied considerably at short intervals in the same patient. On a number of occasions with a systolic pressure of 170 mm. Hg. it was impossible at one moment to hear the Korotkov sounds, while a few seconds or minutes later the sounds were loud and clear; such variations bore no apparent constant relationship to respiration.

The subsequent course of these patients varied. In two boys with severe injuries to an arm, the systolic pressure remained about 140 mm. Hg. Both cases had the arm amputated above the elbow

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and little blood was lost before or during operation. In each case at operation the injured brachial artery was seen to be firmly constricted and cord-like. When blood or plasma loss continued, or restarted after warming or during operation, the systolic and diastolic pressures fell suddenly to very low levels. Mild hypertension sometimes passed off after the patient had been warmed and given a sedative, but if warming was excessive a marked fall in pressure was precipitated. In no case did hypertension last for more than eight hours. Hypertension was also occasionally produced in adults by the transfusion of 500 to 1000 c.c. of blood or plasma in five to fifteen minutes. The elevation of the systolic pressure was usually transient, the level falling steadily to below 120 mm. Hg. unless further fluid was transfused at a fast drip rate.

It has been observed repeatedly that when a patient whose blood pressure is too low to be estimated is transfused rapidly, the systolic pressure may first be measurable either at about 60 to 80 mm. or at over 130 mm. Hg.; as more fluid is given this high systolic level usually falls to within normal limits provided that blood or plasma is not lost from the body. Further fluid loss may cause hypotension to recur, and if the rate of loss exceeds that of replacement the systolic level may again fall to a very low level.

Respiratory Variations

A phasic variation in systolic pressure of 5 to 20 mm. Hg., beginning towards the end of inspiration and lasting until nearly the end of expiration, was found in association with severe shock; its appearance commonly preceded or accompanied a fall of pressure or followed rapid transfusion. This feature lasted sometimes for only a few minutes, but on other occasions for as long as an hour or more, depending on the changes which were taking place in the circulation.

Colour, Temperature and Humidity of Skin

At the same time as blood pressure was estimated the state of the skin of the ears, nose, hands and feet was noted. The changes found depended on the severity and duration of the systemic disturbance and on the environment of the part examined. Very high or very low blood pressure was usually associated with pallor. Cyanosis was found when shock was of great severity and duration. The temperature of the part examined had an important bearing on colour and varied with environment. At ordinary ward temperature the exposed parts of the shocked patient are usually cold, and pallor or cyanosis, if present, are most marked in those areas. If one arm and hand remained exposed for transfusion or blood pressure estimations, pallor or cyanosis persisted, and skin temperature remained low in that hand long after the covered extremities had become warm and

red. The nose and, to a less degree, the ear-lobes were also apt to be misleading because of cooling, and it was essential that observations on the state of the skin and capillary circulation be made at several points with different environments.

In the normal subject colour returns almost immediately after compression of the nail-beds of the fingers or toes. In very severe shock the return of colour may take five or more seconds. These observations were of value if used in conjunction with other data such as the blood pressure levels. Other factors aside, a low blood pressure associated with good peripheral colour and rapid return after compression was less ominous than similar pressures with cyanosis, pallor and delayed colour return; other factors being equal, delayed return alone was of significance. After fluid replacement, an elevation of pressure which was not soon followed by an improvement in pallor or cyanosis or an acceleration of colour return was indication for caution, and was strongly suggestive of inadequate transfusion or continued bleeding.

Sweating has always been a prominent feature of classical descriptions of the shocked patient, but in many of the present series of cases sweating was not found at any time during even very severe degrees of shock, and in others its incidence was subject to great variation. Sweating, like skin colour and temperature, was influenced considerably by environment. On admission in severe shock all parts of the patient's skin might be cold and clammy; on warming the unexposed areas recovered first and became warm, and later dry. After excessive heating the face and brow became pale and beaded with sweat and the lips became cyanosed, an exposed hand was cold and clammy but the patient complained of the excessive heat. Unless covered parts such as the legs or the trunk were examined, it was not appreciated that in such areas there was maximum vasodilation with a hot moist skin, heating was continued and death was accelerated. Sweat accumulates particularly on the brow, lips and chin. As a rule, patients suffering from head injuries did not sweat and their skin was warm and of a good colour.

Discussion

There is good reason to believe that the most important initiating factor in shock following tissue trauma is reduction of blood volume, due to local loss of fluid, both external and internal. Success in treatment demands early, adequate and rapid replacement of this lost fluid by the transfusion of whole blood or plasma; in addition to such surgical treatment as may be necessary. The ideal is to diagnose shock in what at present is termed the " incipient " stage, before there are measurable alterations in blood pressure and blood composition. The characteristic vascular pressure pulses and venous pressure changes observed by Wiggers (1942) in animals in incipient shock, are of no value since similar changes are found in other conditions.

At later stages progressive decline in central venous pressure, cardiac output and arterial pressure have been observed in animals, and provide good indices of the severity and rate of progression in shock. Blood pressure alone of these features can be readily measured at the bedside, but it provides a limited picture of the clinical condition of the patient. Coincident observations of changes in the circulation in the superficial skin vessels give additional information.

Adequate replacement implies the transfusion of a volume and type of fluid equal to the external loss from the circulation. An estimate of the quantity required is made partly from a detailed history of the amount of fluid lost, combined with observations of the injuries, dressings and clothing and partly on the observed response to treatment. The amount varies with each patient and depends on factors such as age, body weight and the amount lost. The rate of transfusion is of prime importance and replacement should be as rapid as can be tolerated. Toleration and requirement can be assessed directly by observation of the effects of transfusion. The time factor is of vital importance in shock, and for this reason clinical methods of assessment must be capable of easy and rapid measurement. The methods of determining blood volume at present available are neither sufficiently convenient nor accurate to be of value. The observations of Grant and Reeve (1941) suggest that, apart from thermal injuries, hæmoglobin estimations also are of little value in the early stages of shock.

The majority of injured patients must be prepared for further treatment, which involves further trauma and the risk of a recurrence of shock. In the presence of extensive injuries, intense compensatory vasoconstriction combined with fluid loss leads to temporary cessation of blood or plasma loss. Transfusion (by partially restoring blood volume), or to a lesser degree excessive warmth (by releasing constriction) may restart fluid loss; the rate of this loss may equal or exceed that of replacement. Under these circumstances the surgeon has to make a most difficult and important decision. Is transfusion to be continued in the hope that further improvement can be obtained before operative treatment of the injuries is begun; or does immediate local treatment of the injuries, in spite of the existence of a severe degree of shock, offer a better chance of survival to the patient? Transfusion may fail to produce the expected improvement, and operation must then be undertaken, as a last resort on a patient whose condition has been deteriorating for some time. Operative treatment carried out in the presence of severe shock increases the liability to sudden collapse beyond the reach of resuscitation. For each severely injured patient there is an optimum time for treatment, which may be fleeting and comes once only; when this opportunity is missed, it is impossible to obtain as good a response again.

Resuscitation, therefore, should be carried out under the direct supervision of the surgeon, and the operation timed to correspond with, or slightly to anticipate the peak of improvement. This peak in

general condition can best be gauged by the close observation of the effects of transfusion and other restorative measures, as shown by changes in skin colour, blood pressure, mental state and the rate and amount of blood or plasma loss from the injured parts. The severely injured patient has a limited tolerance to further trauma, surgical or otherwise. The minimum of surgery that is essential is all that should be undertaken, and this also must receive due consideration in assessing the fitness of the patient for operation.

In the past, the diastolic blood pressure has received but slight attention in the investigation of shock. The diastolic level varies directly with changes in peripheral resistance, blood volume, heart output and blood viscosity, and by its measurement additional information may be obtained of the state of the vascular system. In order to assess the relative importance of each of these factors in a particular case, knowledge is required of the amount of blood or plasma lost, the duration of the injuries and the state of the circulation in the main vessels and in the capillaries.

At all times there is tonic constriction of the blood vessels, which varies in degree according to the requirements of the tissue supplied, the environment, and the circulating blood volume. After gross reduction of blood volume, the vessels of certain tissues, such as the skin, constrict in an attempt to maintain an adequate circulation in the vital organs, heart, brain and lungs. The volume of blood going to the limbs is limited and the vessels of the limbs are constricted. Under these circumstances, a high systolic pressure may be associated with a high diastolic and low pulse pressure, an imperceptible radial pulse, barely audible Korotkov sounds and marked respiratory variation. When constriction and hypotension coexist, a significant but transient elevation of systolic and diastolic pressures may follow the transfusion of a relatively small volume of fluid. Following the rapid transfusion of a large volume of fluid, hypertension may develop, presumably because overfilling occurs before intense constriction has had time to moderate. Marked constriction is accompanied by pallor and may affect veins as well as the arteries and arterioles; even a large vein such as the internal saphenous, when exposed for cannulation, is sometimes found to be tightly constricted with a hair-like lumen, in contradistinction to the classical descriptions of collapsed veins. It is impossible to puncture such a vein successfully with a transfusion needle and frequently the insertion of a cannula is very difficult.

It is generally accepted that the end of the fourth sound of Korotkov indicates when a pulsatile or intermittent flow of blood beneath the cuff becomes a continuous stream. When this sound can still be heard after complete deflation of the cuff or at very low pressure (*e.g.* 5 to 20 mm. Hg.) it seems reasonable to conclude that the blood flow retains its intermittent character at very low pressure levels. This may be the result of loss of elasticity of the vessel wall by reason of

very intense constriction with consequent failure to distend; imperfect filling due to reduced blood volume and heart output, the volume of the contained blood being sufficient to distend the vessel wall; dilation of the smaller peripheral vessels, or to a combination of these factors.

The arbitrary classification of patients according to their blood pressure levels was employed during the Great War by Fraser and Cowell (1917), who described two groups, hypertensive with systolic pressures of 150 to 170 mm. Hg. and hypotensive with systolic pressures of 40 to 90 mm. Hg. In many of their hypertensive patients, after resting and transfer to a C.C.S., the pressure fell to 110 to 120 mm. Hg. and remained at that level. Hypertension was frequently associated with injuries of the ventricles of the brain with raised intracranial pressure or with compound fractures of the skull with an intact dura. The patients with ventricular injury were prone to sudden post-operative collapse in a state "which clinically resembled acute shock," which was attributed to the combined effects of ether anæsthesia and wide opening of the skull. This type of collapse was avoided by delaying operation for twenty-four to forty-eight hours, or by the use of local anæsthesia and morphine-scopolamine narcosis if immediate operation was essential. This suggests that ether anæsthesia may have been the chief factor concerned, presumably by causing generalised vasodilation and sweating. Subsequently, Fraser and Cowell abandoned blood pressure in favour of severity of injury as the basis for classification of shock.

Hypertension is a rare but important feature of shock, its occasional occurrence in air raid casualties has been described by Grant and Reeve (1941). When found in the early stages it is an indication of compensatory constriction. This may pass off during warming or anæsthesia, to be followed by either a sudden and severe fall of blood pressure to a subnormal level or a gradual fall to a level within limits. Hypertension following rapid transfusion indicates that the volume of fluid administered has overfilled the spastic vessels. Close observation is necessary in both types if a sudden fall in pressure is to be detected. In association with severe injury, a blood pressure within normal limits (systolic 100 to 120 mm. Hg.) should be regarded as potentially hypertensive and treated accordingly. Hypertension is probably more common in children than is generally believed, since the systolic level of 20 to 60 mm. Hg. at birth may attain to 80 mm. Hg. after one month, and thereafter rises more slowly to 100 mg. Hg. at the age of 12 years (Meakins, 1927). The application of adult standards of normal systolic/diastolic of 120/70 mm. Hg. will mask a number of hypertensive responses.

The phasic variation in blood pressure, also reported by Grant and Reeve (1941), affects only the systolic level and, beginning towards the end of inspiration, is maximal during expiration. It is associated with severe loss of blood or plasma, often heralds a fall in pressure, and occurs also during transfusion. A possible explanation is based

on the normal increase in left ventricular filling in the terminal part of the inspiratory phase and the earlier part of expiration. In the normal subject this variation affects both systolic and diastolic levels. When the circulating blood volume is greatly reduced, this respiratory increase is also much reduced and affects only the systolic pressure level. This limited measurable effect is believed to be due to the inertia of the sphygmomanometer. Similarly, when only the first Korotkov sound is audible, it is possible that the absence of the other sounds is due to the small stroke volume of the heart which cannot produce an audible effect during the diastolic phase.

When systolic and diastolic pressures fall to very low levels the character of the blood flow in a wound changes. A cut artery no longer spurts but produces a thin stream, and from a vein there is a sluggish flow of a little dark blood which soon ceases; both these ominous features indicate a low blood pressure and diminished peripheral flow, due to a greatly reduced blood volume. Similarly, the ooze of plasma from a burned surface diminishes and finally ceases. Blood pressure alone is of limited value as a criterion of shock; when combined with other observations it appears to be the best clinical method of following the changes which are occurring in a shocked patient.

The quality and depth of skin colour are dependent on the nature of the blood flow in the subpapillary venous plexus (Lewis, 1927). The return of colour after compression of a finger or a nail-bed is due to refilling of this plexus. The temperature of the skin is largely dependent on the rate of blood flow through its vessels and to a lesser degree on the environmental temperature and humidity. Cyanotic or pale skin is usually cold, but may be warm if the circulation in the deep vessels of the part is rapid (but this is unusual in shock). Red skin is usually warm.

Sweating is a variable feature of severely injured persons, and when present must be related to the nature and duration of the injuries and any treatment which has been applied. It is fairly constantly found in very severe and rapidly fatal injuries in association with extreme pallor and coldness of the skin. This would appear to be due to an intense sympathetic response. Sweating cools the skin which in turn causes vasoconstriction, and in shock this is an added protection. It is important to realise that protective sweating may be marked in some areas, such as the face and exposed hands, but absent in others which are under cover, and that environment probably plays a large part in determining whether sweating is evident or not. Sweating deserves further investigation.

A quantitative method of assessing the state of the peripheral circulation, the hyperæmia ring test, has recently been employed by Di Palma (1942), and has proved of value in the diagnosis of severe shock. It does not appear to have made possible the diagnosis of shock in the incipient stage before the blood pressure falls. At

present there appears to be no method by which a diagnosis can be made at this stage. The best that can be done is to try to anticipate shock by preventive measures in the case of those injuries which are known to cause severe shock. Skin changes are of value in recognising and differentiating between shock due to neurogenic factors and that due to blood or plasma loss. It must be remembered, however, that neurogenic factors (vasodilation-warm, red skin) may predominate at first, but later, as the result of further loss of blood or plasma, the picture may change to that of vasoconstriction with a pallid cool skin.

In a clinical investigation of this nature, it is difficult to attribute accurately the cause of all the features observed; some were undoubtedly due to treatment. Variations in the appearance and behaviour are dependent to some extent on the nature and severity of the injury, but to a much greater degree on the stage in the shock process at which the patient is observed. The classical picture is associated with very severe injury and established shock, but it may also accompany an intense vasoconstrictive type of reaction to lesser injury. Restlessness, volubility, irrational demands and other mental disturbances are probably due to cerebral anoxia. These varied manifestations are incidental features in the development of shock and must be recognised as such when associated with severe injury.

Prolonged physical and mental stimulation sufficient to produce fatigue were stated to cause reduction of normal systolic, diastolic and pulse pressures in French soldiers during the Great War; this was also observed in British soldiers by Fraser and Cowell (1917). After prolonged mental and physical rest the pressures tended to rise. Repeated disturbance of the conscious patient, inseparable from frequent observations of the skin and blood pressure, may have an adverse effect on his progress; interference of this kind must be reduced to a minimum. Except during rapid transfusion and operation, half-hourly or hourly observations are usually sufficient. Large doses of morphine, by causing medullary depression, will increase any anoxia already present and thus alter the clinical features to an appreciable degree. Overheating is harmful, leading to vasodilation in the periphery where increased vascularity is less essential than in the central nervous system, heart and lungs, and causing deepening of shock or sudden circulatory collapse. Time is significant in its relation to the cycle of changes, but arbitrary classification of types of shock on a time basis is futile. The type of causal mechanism will provide a more appropriate and productive field of inquiry.

Summary and Conclusion

1. A clinical study has been made of more than 100 patients suffering from the effects of severe accidental injury or operation with special regard to the early diagnosis and assessment of the severity and course of shock.

2. The classical description of shock does not fit every shocked patient; three other varieties of clinical appearance have been described.

3. The combination of serial estimations of systolic and diastolic blood pressure with other simultaneous observations of capillary circulation, blood or plasma loss, consideration of the nature, extent and duration of the injuries, and of such treatment as has been given appear to offer the most convenient and accurate basis for the rapid assessment of the general condition of the shocked patient.

4. Serial observations are essential if the progress, rate and direction of change in the patient's condition are to be accurately followed.

5. Patients were classified according to their systolic blood pressure level. It is emphasised that blood pressure estimation alone is of limited value, even when both systolic and diastolic levels are measured. The systolic level alone is of negligible value.

6. Explanations have been put forward for certain features of shock; such as phasic respiratory variation of systolic pressure and persistence of the fourth Korotkov sound to very low levels.

7. There is very wide scope for the bedside investigation of the clinical features of shock, for example, the variability of sweating, changes in capillary circulation.

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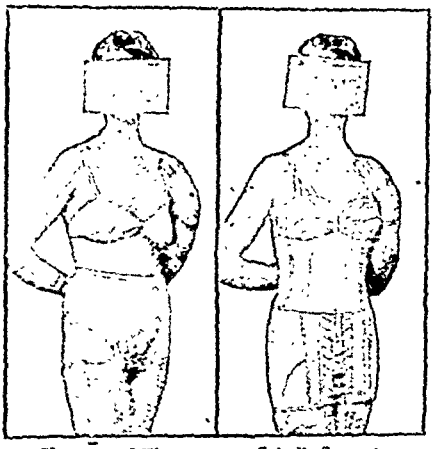

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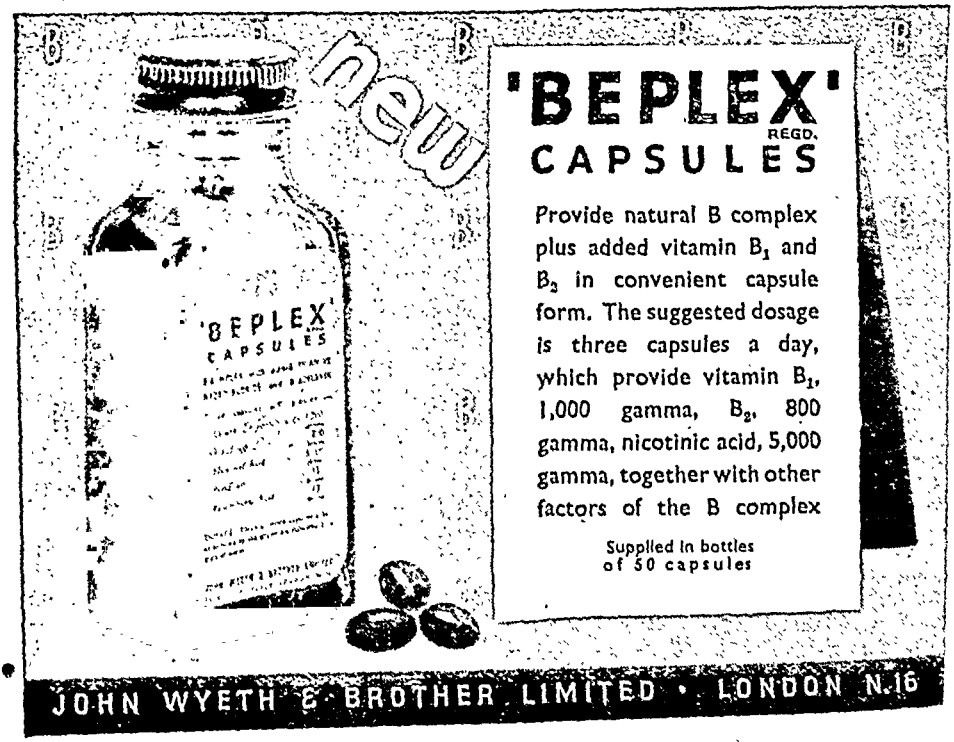

THE PROBLEM OF THE STIFF KNEE JOINT IN FRACTURE OF THE SHAFT OF THE FEMUR*

By I. S. SMILLIE

Orthopædic Surgeon, Scottish Emergency Medical Service

Loss of flexion at the knee constitutes one of the most serious problems which arise directly as a result of the major injuries of the joint, and indirectly as a complication of fractures throughout the entire length of the femur. It is my intention to confine my remarks to the latter problem only, restricting the scope of this lecture to the stiff knee in relation to simple fractures of the shaft of the femur.

Of those who seek the aid of an orthopædic surgeon in the months or years following a fracture of the femur, the majority suffer from loss of flexion at the knee joint or shortening of the limb of a degree sufficient to cause an unsightly limp and disability, with consequent loss of earning power in the labour market. To the working man, and especially the miner, the more important of these disabilities is loss of flexion, and there can be little doubt in the mind of a miner that an inch of shortening is preferable to a stiff knee. Observation of the arduous conditions under which miners work makes it only too evident that a loss of even twenty degrees of flexion constitutes a severe handicap. In this respect I would go so far as to say that no surgeon who undertakes the treatment of fractures of the shaft of the femur has completed his training until he has worked a shift at the coal-face. There are few whose respect for the integrity of the knee joint would not be increased.

I am aware that there are some surgeons who deny that this problem really exists. They state that their fractures do not get stiff knees. My experience of the treatment of the 150 femurs for which I have been responsible since June 1940, and of the examination of an even greater number referred from military convalescent depots and at a civilian rehabilitation centre, shows that the problem is one common to all surgeons. From this not inconsiderable number of cases I have learned much, both from my own mistakes and from the mistakes of others, and in the course of this lecture I hope to show that although there are certain cases in which residual stiffness is inevitable, very many cases exist in which the responsibility for the loss of movement lies not in the nature of the fracture but in the treatment.

* A Honyman Gillespie Lecture, delivered in the Royal Infirmary of Edinburgh, 19th April 1945.

Developmental and Anatomical Considerations

Before proceeding to discuss the preventative measures which may be taken in the course of treatment to ensure the maximum range of movement in the final result, and to describe the procedures which are available for the treatment of those cases in which loss of movement is established, it is necessary to recall some of the factors which are peculiar to the knee joint which make it especially susceptible to residual stiffness.

The knee is not only the largest joint, but the highest in the developmental scale in the human frame. The ability to produce complete extension, which enables us to run, walk and stand, is perhaps the most interesting and important developmental differentiation between man the lower mammals. It is an attribute common only to man. Even the higher apes prefer to walk with the knees slightly flexed, and with the balance afforded by one or both fore limbs. The assumption of orthograde posture is undoubtedly an effort.

To maintain knee extension for the erect posture in man, no new muscles have been evolved. Orthograde functions have been superimposed on the quadriceps which in other mammals performs plantigrade motion. This particular attribute of the knee joint, and of the action of the quadriceps in attaining it, are both acquisitions of recent biological origin, and, like all recent biological acquisitions, are hence unstable.

In addition to developmental vulnerability, the joint is particularly susceptible to the effect of fibrous tissue reaction because of the complex nature of its structure and mechanics. For example, the axis of rotation, although situated in the posterior aspect of the femoral condyles, is not a fixed point, but moves forward in flexion and backwards in extension as a result of the gliding movement which is superimposed upon the hinge action; in flexion, not only must the medial collateral ligament glide freely on the femoral and tibial condyles, but the patella must move through a distance as great as three inches. To permit such free excursion of the interrelated supporting structures, the joint is surrounded by the largest and most extensive synovial membrane and capsule in the body. Adhesions in relation to any portion of the synovial cavity or capsule must restrict free movement of this complex joint.

I would mention one further point in the structure of the joint which directly concerns our problem. In the development of joints there appears to be a tendency towards an increase of secretory areas and a reduction of simple connective tissue lining. In the knee joint the synovial fluid is elaborated in special cells which are situated over the four fat pads [1]—(1) the infrapatellar, (2) posterior suprapatellar, (3) anterior suprapatellar and (4) the popliteal, and over the loose connective tissue with its folds and villi. Fibrous tissue replacement of any of these areas greatly reduces the production of synovial fluid.

PREVENTION

Adhesions which produce limitation of movement may be situated :—

(1) *Within the joint cavity*; the areas most frequently affected are the suprapatellar pouch, and the medial and lateral joint compartments.

(2) *In the capsular and extracapsular tissues*; the areas most frequently affected are the lateral and medial expansions.

(3) *In the lower third of the quadriceps*; as a result of the adhesion of the components of this compound muscle to one another and to the femoral shaft which follows the direct injury to muscle which almost inevitably accompanies supracondylar and especially high supracondylar fractures.

I have already stated that residual stiffness may be due to the treatment employed. The results of treatment in cases in which loss of flexion is already established seldom bear comparison with the range of movement of the normal joint. It is therefore my intention to devote the greater part of the time available to a consideration of the merits and demerits of methods of treatment which are in common use, with special reference to the preservation of the maximum range of movement in the final result.

Let us consider the subject of prevention under three headings :—

(1) THE VIOLENCE WHICH PRODUCES THE FRACTURE ALSO INJURES THE JOINT.—The injury takes place most frequently as a result of direct violence. It requires no stretch of the imagination to appreciate that force applied to the lateral aspect of the thigh of sufficient magnitude to produce a fracture within the strong lower third of the bone, produces considerable strain on the knee joint prior to the occurrence of the fracture. Critical observation of a series of cases will show that a large proportion of fractures demonstrate the presence of synovial effusion or even hæmarthrosis—convincing evidence that the joint has been subjected to trauma. If the fracture had not occurred, the condition of the joint would have warranted investigation in order to establish an exact diagnosis and institute the appropriate measures, but the magnitude of the major fracture overhadows the knee joint injury, which is often disregarded in both the selection and execution of treatment. The treatment adopted, be it skin extension or even traction transmitted by a Steinman pin to the fracture site through the injured joint, may produce anatomical reduction and eventually sound union, but ignores the effect which such methods may produce on the future function of the knee joint.

(2) METHODS OF TREATMENT PREJUDICIAL TO THE WELFARE OF THE KNEE JOINT.—Under this heading I would like you to note that no matter which of the many available methods is chosen, union

of a soundness which will permit weight-bearing is seldom established in less than three months. An uninjured joint, provided it is not fixed in a position of strain, is little affected by such a period of immobilisation; this is demonstrated by the rapid return of full flexion which follows removal of the thigh length plaster cast used in the common fractures of the shaft of the tibia. There must, therefore, be other factors unfavourable to the return of movement in addition to the effect of immobilisation alone. Unfortunately, these factors, of which by far the most important is powerful traction, are often in force for periods much greater than three months, and it is not uncommon for union to be delayed as long as nine to twelve months in an apparently uncomplicated case.

Powerful Traction.—I have mentioned powerful traction as the most important factor. Let me consider it first. In his presidential address [2] to the British Orthopædic Association, Mr Girdlestone said: "There has always been a potentially harmful factor inherent in the method of weight and pulley traction; but much actual harm has been done since skeletal traction has made it possible to use heavier weights and to leave them at work for longer periods."

Prolonged powerful traction is often prolonged merely because it is powerful. In addition to delaying the progress of union, it produces a most damaging effect on the joint both by reason of its power and the time through which it continues to act. The capsular and extra-capsular adhesions which follow are due to direct irritation of the supporting structures, whereas the intra-articular adhesions in the suprapatellar pouch, and in the medial and lateral joint compartments, may possibly result from inhibition of the production of synovial fluid, or even to the replacement of the secretory areas by fibrous tissue. Who has ever seen a stiff knee joint with a synovial effusion?

In contra-distinction, the use of continuous traction of five to seven pounds is consistent with rapid return of function. Most important of all is that the traction should not be expected to reduce the fracture, but merely to assist in maintaining the accurate reduction secured manually by the surgeon.

Skeletal Traction.—The prolonged powerful traction made possible by skeletal traction leads naturally to mention of a method of skeletal traction which is of itself detrimental to the knee joint. I refer to the use of a Kirschner wire or Steinman pin passed through the condylar or supracondylar regions. Infection of the pin track is frequently unavoidable with consequent inflammatory reaction in the adjacent suprapatellar pouch. In two cases which came to operation as a result of persistent stiffness I have encountered walled-off abscesses containing sterile pus in the suprapatellar pouch, and in a third case a similar abscess was found in the quadriceps; in no case was there any evidence of gross infection of the pin tract. Even in the absence of recognisable infection, the prolonged association of a metallic foreign body with this large area of synovial membrane sets up an

aseptic inflammatory reaction, the outcome of which is the complete obliteration of the pouch. In this respect it would seem that the Kirschner wire, in spite of its narrow gauge, is productive of more reaction than a Steinman pin. The Kirschner wire is drilled through the bone and therefore of less diameter than the hole through which it passes, and, being firmly clamped to the accompanying stirrup, is subject to transmitted rotary movement. The Steinman pin is driven through the bone and is therefore for some considerable time a perfectly tight fit; it is not subject to transmitted rotary movement from the Bohler type of stirrup. It is not unreasonable to suggest that if, for mechanical reasons, skeletal traction through the lower end of the femur is considered essential, the method of choice is a Steinman pin and Bohler stirrup, which must be changed in favour of some other method of maintaining reduction within the space of three weeks if the integrity of the suprapatellar pouch is to be respected.

Operation.—Next, let us consider operative measures which are prejudicial to the joint.

When the decision is made to resort to open reduction and internal fixation, it is essential to adopt a technique calculated to secure sound union in the minimum time and with the maximum regard for the future function of the extensor apparatus and the integrity of the joint. The use, for example, of the anterior midline incision is indefensible, for it respects neither the anatomy nor the physiology of the quadriceps muscle. Patients are still encountered in physiotherapy departments and rehabilitation centres struggling to secure a few degrees of flexion against the overwhelming odds produced by adhesion of the rectus femoris and vastus intermedius to the bone, and the complete obliteration of the suprapatellar pouch. With regard to the methods of internal fixation applicable to the recent case, it is only necessary to say that only non-toxic stainless steel should be used. The screws must be of the same material as the plate and must engage the cortex on the medial aspect of the femur.

Bone Grafting.—Bone grafting operations are usually undertaken as a last resort when the knee joint has already been subjected to prolonged traction and immobilisation. For this reason it is rare in my experience to encounter a grafted femur in which the range of motion in the knee is not severely restricted. I hope to show you that it should be possible to anticipate delayed or non-union, and thus avoid employing the useful procedure of bone grafting only as a last resort. If the patient is subjected to bone grafting the actual technique is important. The temptation to use the technically simple but physiologically unsound intramedullary bone peg must be resisted. The massive onlay graft, secured by stainless steel screws, offers the best prospects of union in the shortest possible time.

(3) ERRORS IN THE COURSE OF TREATMENT.—My third heading brings up the whole question of the selection of the method of treatment to be adopted in the various types of fracture. There is no single

method which can be applied to all types. Each fracture presents a different problem. Each individual surgeon has his favourite methods, and it is well established that it is not the method which is responsible for the good or bad result so much as the skill and attention of the surgeon who uses it.

I would like to point out, however, that in selecting the method of treatment suitable to a particular fracture it is essential to aim at the ideal of securing sound union in the shortest possible time. In order to attain this ideal it is frequently necessary to reconsider the original decision and change the procedure within the first week if the reduction and stabilisation of the fragments is not of a sufficiently high standard. If, for example, in a fracture in the middle third of the shaft, skin extension in a Thomas splint is the method of treatment adopted, the prospects of rapid union should be assessed when it is considered that the best possible reduction has been obtained. If there is uncorrected angulation still present, with or without distraction at the fracture site, union will at best be delayed. It is thus better to make the voluntary decision to carry out accurate operative reduction and the insertion of a vitallium plate or massive onlay graft than wait for six to twelve months for consolidation to occur, or be forced to insert an onlay graft after a delay of six months, in order to secure union. Such prolongation of immobilisation invariably causes some permanent loss of flexion in the knee joint.

Methods of Treatment

At this point I would like to show you the methods of treatment which I use and which are the result of the experience of some 150 cases. These particular methods have been chosen to secure the most rapid union, considering the different problems which fractures in each of the thirds of the femur present.

(1) Fractures within the Lower Third.—This group, which includes the supracondylar fracture, is the most difficult of the three from the point of view of return of knee flexion, because the injury often involves the knee joint directly by penetrating the suprapatellar pouch, and the quadriceps is invariably damaged in some degree. If the vastus intermedius is seriously injured, loss of flexion, and sometimes even of extension, is inevitable no matter how perfect the reduction and after-treatment.

The displacement in the supracondylar fracture, and, for that matter, in all fractures within the lower third, is characteristic; the lower fragment is flexed by the gastrocnemius. Watson-Jones [3] has stated recently that this fracture is rare and difficult to reduce by recognised methods. With neither of these points can I concur. It is a common fracture in mining areas, where it occurs as a result of a fall of roof on the outstretched leg when the miner is in the crouched position, and although I have already said that loss of flexion may be inevitable, I find it the most simple and certain of all fractures of the

femur, both to reduce and in which to obtain rapid union. The fracture is reduced by strong manual traction and manipulation in flexion, and immobilised on the Braun-type splint with the angle placed at the fracture site rather than at the knee joint. The reduction is maintained by 5-10 lb. of traction applied through a Steinman pin driven through the tibial tubercle. Weekly X-rays and daily adjustment of the pad of wool at the angle of the splint are necessary for at least six weeks. At the sixth or eigth week the limb is transferred to a Thomas splint and the skeletal traction discarded in favour of skin extension. The limb should not be kept in the flexed knee splint any longer than is necessary, because vastus medialis exercises are impossible in any splint which immobilises the knee in more than 15° of flexion. This is particularly important in a fracture in which the danger of adhesion of the vastus intermedius to bone, and of the other components of the quadriceps to one another exists. The secret of success, as in all fractures of the femur, is to secure reduction by manual traction and manipulation. If heavy weight and pulley traction is expected to produce the reduction, the method will fail.

(2) FRACTURES IN THE MIDDLE THIRD—the most common of the fractures of shaft. The Thomas splint with skin extension, and fixed or weight traction, is the method advocated in this region, the reduction being secured, as in the distal third, by mannual traction and manipulation, and merely maintained by 5-10 lb. of extension. If the reduction is imperfect, especially in the form of uncorrected angulation which leaves a wide gap at the open aspect of the angle, possible interposition of soft tissues or distraction at the fracture site, union at best will be considerably delayed. In these circumstances it is far better to change the method, and resort to open operation and the insertion of a stainless steel plate or massive onlay graft. This decision is made at the end of the first week, and not deferred for three months, when it is quite evident that the case is one of delayed or non-union.

(3) FRACTURES IN THE UPPER THIRD.—This injury is fortunately uncommon because it is particularly difficult to treat by closed methods. The upper fragment is flexed, abducted and externally rotated; it is no simple matter to bring the large mass of bone and muscle which constitute the lower fragment into line with it. This is the fracture which is responsible for the most gross degrees of malunion and shortening which are encountered. I consider that the method of choice in this particular fracture is open reduction and internal fixation with a stainless steel plate.

REHABILITATION

It is not possible to complete the section on the prevention of knee stiffness without mention of after-treatment or rehabilitation. Fractures of the shaft of the femur are seldom considered to be welcome admissions to a general surgical ward. The lack of enthusiasm with

which they are received is partly due to the lengthy and undramatic nature of the treatment required, and partly to the necessity for the large amount of care and attention which is seldom lavished upon them. This is unfortunate, for it is only in an atmosphere of enthusiasm that wasting of morale and muscle, which has such an evil effect on the final result of this potentially crippling injury, can be avoided.

Rehabilitation does not begin when it is already obvious that the patient has permanent loss of flexion. It should begin as soon as the reduction of the fracture is adjudged to be satisfactory, and the position of the fragments stabilised. Early direct knee flexion exercises are only possible by the use of such methods as fixed extension in a Thomas splint incorporating a knee flexion piece, or following rigid internal fixation, but there is no method of immobilisation in common use which will not permit the tone and volume of the extensor apparatus, and the anterior and posterior groups of tibial muscles to be maintained. Knee flexion returns most rapidly in a limb in which the maximum muscle volume and tone have been preserved. Moreover, the normal mobility of the patella, on which the return of flexion so largely depends, may be retained not only by quadriceps drill but by passive movements in a superior, inferior, lateral and medial direction, practised by the patient himself at hourly intervals throughout the day.

When immobilisation has been completed, recovery of movement is produced by regular active exercise. The only other physiotherapeutic measure which is permitted is radiant heat, provided it is clearly understood by the patient, and by the supervising physiotherapist also, that radiant heat has no curative value without subsequent exercise.

It is especially important to realise that in the early stages of recovery no treatment is productive of more damage than vigorous passive exercises in the hands of an over-enthusiastic masseuse, or early manipulation of the knee joint under anæsthesia. It is better to forbid "the laying on of hands" than risk the permanent disability which may follow "pump handling" of the joint. The knee, like the elbow joint, registers protest to such treatment by progressive increase of stiffness.

Treatment of Established Loss of Flexion

I have employed most of the time available on preventive measures, and have left little time for the mention of the methods of treatment available in established loss of flexion. This is as it should be; for, as in all medical matters, the prevention of a disaster is more important and produces better results when successful than the best result which can be produced from treatment of the disaster once it has occurred.

Established loss of flexion, as we have already seen, is due to the formation of fibrous tissue within the joint, capsule and extra-capsular tissues, or in the muscles controlling the joint. In the worst cases adhesions may be present in both the joint and in the controlling muscles.

Manipulation under anæsthesia is the most satisfactory method available for the treatment of established loss of flexion. Unfortunately, it is a method only applicable to capsular and extra-capsular adhesions. It is useless, and indeed may result in additional damage, if applied to cases in which the suprapatellar pouch is obliterated, or the quadriceps bound down to the femur. Moreover, it is a procedure which is only indicated when the range of movement in the joint is no longer increasing by the patient's own active exercise. The success or failure of manipulation depends entirely upon the meticulous care with which patients are selected. So much harm may follow manipulation of the unsuitable case, or the suitable case at the wrong time, that I propose to enumerate the contra-indications rather than the indications. Manipulation is contra-indicated :—

(1) *In the presence of any active pathological process*, in orthopædic parlance, in the presence of a "hot joint." Swelling and increase of local temperature in the periarticular tissues indicate the presence of a reactionary exudate which will be further increased by the trauma of manipulation.

(2) *In the early stages of recovery*. It should not be contemplated until the maximum range of movement has been obtained by regular active exercise, that is to say, until improvement, accurately measured by angle-meter, has been stationary for at least six weeks.

(3) *In the presence of decalcification of the femoral condyles or patella*. If manipulation is performed in the presence of osteoporosis, not only is additional risk of injury to the patella incurred, but crush fractures of the tibial condyles may take place as a result of the weakness of the trabeculæ supporting the articular cartilage. In any marked degree of decalcification the procedure should be deferred until weight-bearing and non-weight-bearing actively increases the calcium content of the bone.

(4) *In the presence of unsound union at the fracture site.*

With experience it is usually possible to assess what success is likely to follow manipulation from the clinical examination of the joint. If the patella is reasonably mobile in all directions and there is no obvious dense fibrosis in the quadriceps or in the suprapatellar pouch, and the resistance at the limit of the range of passive flexion is elastic, the prospects of success are good. If, on the other hand, the patella is tightly bound down by adhesions in the lateral expansions and in the suprapatellar pouch, and palpation of the pouch reveals deep fibrosis, the block at the limit of flexion is usually solid. In these circumstances, the prospects of obtaining any increase of movement, without the use of force of a degree likely to cause rupture of the extensor apparatus, are poor, and plans should be made to

supplement a preliminary closed manipulation with open division of the adhesions before forcible manipulation is attempted.

TECHNIQUE.—In the technique of manipulation which I have evolved, the anæsthetised patient is placed in the supine position on a firm table or plinth. To manipulate the right knee, the surgeon grasps the patient's thigh immediately above the patella with his left hand; this action protects the femur and guards the patella against possible fracture. The right arm is passed under the patient's leg, so that the back of the wrist rests against the posterior aspect of the upper end of the tibia, while he grasps his own left wrist with his right hand. The medial aspect of the surgeon's right upper arm is now in contact with the front of the patient's tibia, permitting powerful but guarded pressure to be exerted by adduction of the shoulder. The only help which should be sought from an assistant is fixation of the patient's pelvis to the table by backward pressure on the iliac crests. He should not hold the limb, or take any active part in the manipulation, as it is impossible for the surgeon to assess what power his assistant is exerting. If the application of pressure at the limit of flexion causes the adhesions in the lateral expansions to break with an audible snap, the operator may proceed carefully to full flexion; but if pressure only produces the gradual tearing of diffuse fibrosis, great care should be observed lest the reaction produced aggravates rather than relieves the stiffness. In these circumstances it is preferable to carry out several gentle manipulations at intervals of one to two months than to produce a violent periarticular reaction which precludes the possibility of active exercise and discourages the patient from the full co-operation which is the essential of success.

After-treatment.—Manipulation is but an incident in the treatment of persistent stiffness. It is valueless unless the range of movement obtained is maintained by active exercises instituted at the earliest possible moment. It is for this reason that the selection of cases is so important. Manipulation of the knee joint in a patient who is disinterested in his own recovery, or who lacks the moral and physical courage to persevere with exercises in spite of discomfort or actual pain, is a waste of effort and will only lead to disappointment.

OPERATION.—I have already stated that when the patella is bound down to the femoral condyles by fibrous tissue in the lateral expansions, and by obliteration of the suprapatellar pouch, manipulation will fail. Attempts to secure an increase of movement by manipulation merely bring a most useful procedure into disrepute. In such cases the only possibility of improvement lies in operative division of the adhesions prior to manipulation. It is necessary, however, to stress once again that the recovery of a useful range of motion in such circumstances is a long and painful process, and treatment should only be considered in patients in whom an increase in the range of flexion is of the utmost importance, and who are fully aware that the operation is merely the prelude to a regime which requires both patience and determination.

The operation is performed through two 1½ in. incisions, one on each side of the superior pole of the patella. The gloved forefinger is passed through each incision in turn, and the fibrous bands running down to the femur and to the head of the tibia localised and broken down, or divided with scissors. A further attempt is now made to flex the joint, when it will usually be found that the adhesions in the suprapatellar pouch are preventing any considerable increase in range of flexion from being obtained. These adhesions are broken down by inserting the forefinger into the pouch, or, if the fibrous tissue is too dense, by means of scissors. When all the restricting fibrous tissue has been severed it is usually possible to flex the joint through 90° or more, the manipulation being accompanied by the breaking of further minor adhesions in the capsule.

The increase in the range of movement obtained by this method varies widely between 10° and 90°, depending on the nature of the local pathology and the determination and fortitude of the patient.

It is clear that the painful and protracted process which follows operation could be modified and curtailed by the interposition of some membrane between the walls of the suprapatellar pouch, and between the lateral expansions and the femoral condyles, which would prevent the inevitable formation of further adhesions. In the last three cases I have introduced a piece of sterilised cellophane, cut in a pattern to fit the suprapatellar pouch and extending medially and laterally on either side of the femoral condyles. In the United States, McKeever [4] has used this method of preventing adhesions following synovectomy, and considers that this substance is inert. I can only say that my results are promising, but I have as yet not enough experience to recommend it without reserve.

Adhesion of the Quadriceps to the Femur

Finally, there remains for us to consider what measures can be taken to increase the range of movement when the obstruction to flexion is due to adhesion of one or other of the components of the quadriceps to the femur and to one another, and in the absence of any gross changes in the joint. This is the condition which, in relation to simple injuries, follows the supracondylar fracture, but is, of course, even more common in compound injuries, and especially in the grave muscle and bony injuries produced by missiles.

The only reparative measure which has undergone an extensive trial is that of Bennet,[5] who aimed at a return of flexion by lengthening the quadriceps tendon. Most observers have expressed disappointment with the results of this operation. This is not surprising, considering the fact that it is not based on an understanding of the underlying pathology. The quadriceps is not shortened ; it is merely adherent to the femur. There is no doubt that the underlying pathology is adherence of the vastus intermedius to bone, or the replacement of that component by fibrous tissue, so that the rectus femoris is fixed.

In some cases, but seldom following simple injuries, both vastus medialis and vastus lateralis may be involved.

Recently Thompson [6] has described a procedure which he states is based on Bennett's operation, but which preserves intact the rectus femoris component of the extensor apparatus, and eliminates the deeper components which are adherent to the femur, or replaced by scar tissue.

The operation is performed through a long anterior incision, and the dissection carried deeply on either side of the rectus femoris, so that both the vastus medialis and the vastus lateralis are completely freed. This gives access to the vastus intermedius, which will usually be found to be infiltrated with fibrous tissue which is binding both the rectus femoris and patella to the surface of the shaft. The vastus intermedius is excised completely, leaving a fibrous and periosteal covering over the front of the bone.

As the rectus has now been entirely freed of scar tissue, and is capable of stretching, especially in the upper normal portion, the knee can be manipulated with safety, and the remaining adhesions broken down.

The result of the intra-articular operation which I have just described, and the final result in this operation, may be prejudiced by the formation of further adhesions. It is for this reason that before suturing the vastus medialis and vastus lateralis back to the rectus femoris I have placed a piece of cellophane between the rectus and the femur.

After-treatment.—At the termination of the operation the patient is splinted in flexion in a Thomas splint with a knee flexion piece. Active flexion and extension exercises, and auto-assisted exercises in a balanced suspension system, are instituted at the earliest possible moment.

This operation should result in the recovery of right-angled flexion in a good proportion of cases. Some sacrifice must be made for such improvement. The vastus medialis component of the quadriceps is responsible for extension through the final fifteen degrees. Interference with its normal attachment may entail loss of the ability to produce complete extension. This is the price which must be paid for the return of flexion.

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SEVERE HÆMORRHAGE FROM THE ASCENDING COLON, TREATED BY LIGATION OF THE ILEO-COLIC ARTERY. REPORT OF A CASE.

By D. L. C. BINGHAM, Lieut.-Col. R.A.M.C.
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SLIGHT or moderate bleeding is a frequent symptom of many diseases of the large bowel, and of itself it rarely gives rise to acute anxiety. Severe hæmorrhage is rare and its treatment difficult. Usually absolute rest, sedation, blood transfusion and chemotherapy are prescribed, and generally the patient recovers. Very rarely, as in the case about to be described, the bleeding is so violent, protracted and unresponsive to expectant measures that operative interference is undertaken in a last desperate attempt to save the patient's life. Experience of such cases is limited by their very rarity, and it therefore seems important to record this case of profuse hæmorrhage from the ascending colon successfully treated by ligation of the ileo-colic artery.

Sergeant D., aged 31, had always been healthy until early in August 1943, when he had an attack of diarrhœa which lasted twelve days. He passed about 10 watery stools per day which did not contain blood or mucus. After an interval of three days of constipation his diarrhœa recurred and lasted for another three weeks. He then became normal and felt perfectly well. His illness had upset him so little that he did not report sick, and he remained on duty.

A month and a half later, on 26.10.43, he was admitted to a C.C.S. with diarrhœa about 10-12 times daily. His stools contained neither blood or mucus, and beyond the inconvenience of his illness he felt quite well. As he did not improve on sulphaguanadine he was evacuated to this hospital on 30.10.44, with a provisional diagnosis of amœbic dysentery.

On admission his general condition was good, his temperature normal, the liver and spleen were not palpable and there was only slight tenderness in both iliac fossæ. Sigmoidoscopy revealed a normal lower rectum, and the swab showed only an indefinite exudate and no amœbæ.

During the next eight days the patient received 84 gms. of sulphaguanidine, and his stools became semi-solid and less frequent. On 6.11.43 he passed two normal stools, but with the second stool there were 2-3 oz. of clotted blood.

On the morning of 7.11.43 he suddenly became much worse, and at about midday he passed three pints of dark blood which contained a few clots. He rapidly became anæmic, and his hæmoglobin at 14.00 hours was found to be only 25 per cent. A blood drip transfusion was started immediately and morphia in adequate doses was administered.

The next morning, 8.11.43, after he had received four pints of blood he felt much better; his pulse was 88, temperature 99·4° F. and hæmoglobin 70 per cent. The blood drip was continued at a slow rate throughout the day, and by evening he had received in all seven pints.

On 9.11.43 he passed two stools of almost pure blood, together amounting to 1½ pints. Both iliac fossæ were tender, sigmoidoscopy revealed that the blood was coming down from somewhere above the lower rectum, and the patient's blood picture was: Hb. 74 per cent., R.B.C. 3·3m., W.B.C. 4500 (P. 79, L. 18, M. 2, E. 1), clotting time 7 minutes, bleeding time 3½ minutes. In view of the continuing hæmorrhage the blood drip transfusion was restarted, three pints being given during that day and night.

On 10.11.43 his general condition was less satisfactory. His pulse had risen to 100, and during the night he had passed large clots of blood, in all amounting to one pint. His abdomen was slightly distended, and it was patent that he was bleeding rapidly and apparently uncontrollably into his bowel. It was therefore decided to attempt to find and ligate or exteriorise the bleeding area.

With this end in view he was transferred to the surgical division at 12.00 hours. The general data were: P. 100, R. 26, T. 99; B.P. 74/?20; blood urea 68 mgms./100 c.c.; hæmoglobin 40 per cent.

The blood drip transfusion was again restarted, and during the afternoon and evening two pints of blood were given. His general condition improved somewhat and his B.P. rose to 90/60.

On 11.11.43 he was no better; bleeding from the bowel was continuing. His hæmoglobin was only 50 per cent. and his blood pressure was 84/?50. After preliminary sedation with morphia and hyoscine operation was carried out.

Operation

1. Sigmoidoscopy. No satisfactory view was obtained of any part of the rectum as blood poured down from above in a continuous black flood.

2. With a blood drip transfusion running, under local infiltration and nerve block anæsthesia, the abdomen was opened through a long right paramedian incision. The cæcum and the whole large bowel were full of blood, which also extended for about four feet into the small intestine. In spite of a most thorough search, the only pathological area found anywhere in the gut was in the first two inches of the ascending colon, the whole circumference of which was slightly thickened (approx. ×2). It was not possible in this region to see the blood in the bowel, and no definite ulcer or pulsating mural vessel could be felt. In view of his very poor general condition and the absolute necessity for doing the minimum compatible with success, the ileo-colic artery was tied and divided between ligatures 1¾ inches from the ileo-cæcal angle. It was a vessel approximately 5 mm. in

diameter, and its ligature resulted in slight blanching of the ascending colon, cæcum and terminal ileum. After watching the area for some minutes the abdomen was closed in layers, and the patient returned to his bed.

Following operation the patient's condition rapidly improved. The next morning the blood drip transfusion was finally stopped, after the very large total amount of 19 pints of blood had been given in five days. His pulse was 94, T. 100·2° F., B.P. 110/65 and hæmoglobin 82 per cent. No further fresh bleeding occurred from his bowel, only stale altered blood being subsequently evacuated.

In spite of repeated sigmoidoscopy, and search and culture of the stools, neither amœbæ nor dysentery bacilli were ever discovered. Nine days after operation he had several loose stools without blood or mucus, and large numbers of Giardia Lamblia were found which rapidly disappeared with the administration of atebrin, gram 0·1 daily for eight days. Coincidentally his stool immediately became normal. In order also to exclude any possibility of there being an amœbic basis to his illness he was later given a full course of emetine.

A month after operation his general condition was excellent, his hæmoglobin concentration was 95 per cent., his stool normal and without occult blood, and he was discharged to the United Kingdom fit and well.

Summary

The history of a case of severe hæmorrhage from ascending colon is recounted. Expectant measures proving unsuccessful, operation was undertaken, and the ileo-colic artery was ligated and divided. No other example of this procedure has been discovered after search of the available literature.

My grateful thanks are offered to my commanding officer, Colonel P. J. Jory, *D.S.O.*, for his advice and encouragement, and also to Corporal F. C. Scott, R.A.M.C., Blood Transfusion Orderly in this hospital, to whose untiring zeal Sergeant D. really owes his life.

NOTES

University of Edinburgh.

At a Graduation Ceremonial held in the McEwan Hall on Wednesday, 11th July 1945, the following degrees were conferred :—

The Degree of Doctor of Medicine :—James Fleming Curr, Scotland, M.B., CH.B., 1932 (*Commended for Thesis*); Raleigh Barclay Lucas, Scotland, M.B., CH.B., 1937 (*In absentiâ*) (*Commended for Thesis*); Arwyn Roberts, Wales, M.B., CH.B., 1924 (*In absentiâ*); Robert Vaughan Thomas, Wales, M.B., CH.B., 1922; David Cook Wilson, Scotland, M.B., CH.B., 1921.

The Degree of Doctor of Philosophy :—Sushil Kumar Basu, M.B., M.SC. (CALCUTTA) (*In absentiâ*).

The Degrees of Bachelor of Medicine and Bachelor of Surgery :—John Dilworth Abbatt, England; Barbara Margaret Adams, England; Roderick Neil Andrew, England; Thomas Burns Anthony, Scotland; Archibald Douglas Bain, Scotland; William Leftwitch Barton, Kenya, East Africa; Alastair David Ross Batchelor, Scotland; Stephen Henry Brunton Blaikie, Scotland; Margaret Helen Grierson Borrowman, Scotland; Malcolm Brown, England; Andrew Douglas Caird, England; Margaret Alexandra Calder, Scotland; Elspeth Stewart Kirkwood Campbell, Scotland; Mercédès Daisy Carvel, Scotland; Alexander Forbes Catto, Scotland; Gwen Smithson Clark, England; Lorna Halsted Cortis-Stanford, England; Lionel Francis Gilbert Cruickshank, Scotland; Alun Davies, Wales; Anne Dollar Gillespie Davies, Wales; Ewan Campbell Kennedy Douglas, Scotland; George Keith Douglas, England; Kenneth Macdonald Douglas, Scotland; Marie-Hélène Doris Douglas, Scotland; Helen Norman Duke, England; David Durie, Scotland; Frances Barrett Early, Scotland; David John Ellison, England; Constance Catherine Forsyth, Scotland (with Honours); Andrew Hunter Fraser, Scotland; Francis Clifford Fraser, Scotland; Doreen Colina Gardner, Scotland; Donald Frederick Gibbs, Scotland; Eric Gilderdale, England; Walter John Gillies, B.A.(CANTAB), Scotland; James Cameron Gould, B.SC., Scotland; John Telfer Gray, Scotland; Agnes Isdale Greig, Scotland; Neville Donovan Gunasekara, Ceylon; Alfred Ian Gunn-Russell, Scotland; Hilary Frances Hoyte Hamilton, England (with Honours); Ian Roberton Henderson, Scotland; Edward Bruce Hendry, B.SC., PH.D., Scotland; Lawrence Wilfrid Hereward, England; Cyril Hyman, Scotland; Hamish Innes, Scotland; Andrew Westwater Irons, Scotland; James Wishart Jackson, Scotland; Walter Crawford Jamieson, Scotland; Evelyn Isobel Craig Jardine, Scotland; George Pearson Jeffrey, Scotland; Thomas Joyce, Scotland; John Kirk, Scotland; Agnew Barry Grange Laing, Scotland; Ian Lindsay, Scotland; Rae Llewelyn Lyon, Scotland; Mary McDonald, Scotland; Andrew MacFarlane, Scotland; Mary Lowe Macfarlane, Northern Rhodesia; George McLaggan McGillivray, Scotland; Joseph McInally, Scotland; Alastair Ballingall McIntosh, Scotland; William Grant McIntosh, Scotland; Donald Greenshields Mackay, Canada; George Lewis Mackay, Scotland; John Ribton Gore Mackessack, England; Janet Lunan McLaren, Canada; Margaret Elizabeth Macnair (*née* Cameron), Scotland; Ranald Stewart McWilliam, Scotland; Alexander Mather, Scotland; Alison Margaret Matheson, Scotland; John Duncan Matthews, England; Nina

Avis Mellon, Barbadoes, B.W.I.; William George Merriman, Scotland; Mary Young Inglis Millar, Scotland; Isobel Lyall Morrison, Scotland; Margaret Munro, B.SC., Scotland; Isobel Jessie Murray, Scotland; Abraham Bert Ostrovsky, Scotland; Katherine Sheila Haye Pattullo (*née* McConnell), Scotland; John Murray Ure Philip, Scotland; Thomas Philip Stroud Powell, Wales (with Honours); Walter Disney Rider, England; Jean Amphillis Ritchie (*née* Wilson), Scotland; William Arthur Thomson Robb, Scotland; Michael Segal, Scotland; Derek Simpson, England; Hugh Melville Sinclair, Scotland; Ian Scott Robertson Sinclair, Scotland (with Honours); Elisabeth Babington Smith, Scotland; Adrien Robert Souyave, Seychelles; Ralph Felix Hesketh Spencer, England; William John Stedman, England; David Dawson Stein, Scotland; Norman Leslie Stokoe, Scotland; Andrew Alexander Buchanan Swan, Scotland; George Swan Taylor, Scotland; Margaret Helen Fleming Turnbull, Scotland; Ian Archibald Waldie, M.A., Scotland; John Rolland Walls, Scotland; Hamish Watson, Scotland; Josephine Alice Coreen Weatherall (*née* Ogston), B.SC., Scotland; Geoffrey George Wells, England; Beatrice Mary Wilson, Scotland.

The Polish School of Medicine at Edinburgh—The Degree of Doctor of Medicine:—Jan Leyberg, M.B., CH.B.(WARSAW); Bronislaw Sedzimir, M.B., CH.B.; Henryk Maslowski, M.B., CH.B.

The Degrees of Bachelor of Medicine and Bachelor of Surgery:—Wanda Janina Bereza-Zajac, Irena Domanska, Andrzej Ettmayer, Stefan Grzybowski, Jerzy Honigsberg, Maria Kreppel-Dobryszycka, Wiktor Markiewicz, Zygmunt Michalowicz, Edward Nakielny, Józef Pienkowski, Olgierd Rymaszewski, Tadeusz Szczesniak, Wladyslaw Aleksander Wielhorski.

Faculty of Medicine: The Cameron Prizes in Practical Therapeutics—Sir Alexander Fleming, M.B., B.S., F.R.C.S., F.R.S., Professor of Bacteriology in the University of London, in recognition of his discovery of Penicillin; and Sir Howard Walter Florey, M.A., M.B., B.S., PH.D., F.R.S., Professor of Pathology in the University of Oxford, in recognition of his work in making possible the clinical application of Penicillin. *The Ettles Scholarship and Leslie Medal*—Ronald Foote Robertson, M.B., CH.B. *The Scottish Association for Medical Education of Women Prize*—Hilary Frances Hoyte Hamilton, M.B., CH.B. *The Mouat Scholarship in the Practice of Physic*—James Scott Robson, M.B., CH.B. *The Buchanan Scholarship in Midwifery and Gynæcology*—Ronald Foote Robertson, M.B., CH.B. *The James Scott Scholarship in Midwifery and Gynæcology*—Arthur David Bethune, M.B., CH.B. *The Dorothy Gilfillan Memorial Prize*—Hilary Frances Hoyte Hamilton, M.B., CH.B. *The Keith Memorial Prize in Systematic Surgery*—Hilary Frances Hoyte Hamilton, M.B., CH.B. *The Beaney Prize in Anatomy and Surgery*—Ian Scott Robertson Sinclair, M.B., CH.B. *The Royal Victoria Hospital Tuberculosis Trust Medal*—Ronald Foote Robertson, M.B., CH.B. *The Annandale Medal in Clinical Surgery*—George Lewis Mackay, M.B., CH.B. *The Murdoch Brown Medal in Clinical Medicine*—Thomas Philip Stroud Powell, M.B., CH.B. *The Murchison Memorial Scholarship in Clinical Medicine*—Hilary Frances Hoyte Hamilton, M.B. CH.B. *The Pattison Prize in Clinical Surgery*—Hilary Frances Hoyte Hamilton, M.B., CH.B. *The Wightman Prize in Clinical Medicine*—William Arthur Thomson Robb, M.B., CH.B. *The Lewis Cameron Post-graduate Prize*—George Dempster, B.SC., M.B., CH.B.

An Address was delivered by the Promotor, Professor Leybourne Stanley Patrick Davidson, B.A., M.D., F.R.C.P.

Royal College of Physicians of Edinburgh.

A QUARTERLY Meeting of the College was held on 17th July, the President, Dr A. Fergus Hewat, in the Chair. Dr Bryce Ramsay Nisbet (Kilmarnock) was introduced and took his seat as a Fellow of the College. Dr Thomas Addis (San Francisco), Dr Wm. Kerr Blackie (Salisbury, S. Rhodesia), Dr Robert Alexander Miller (Grantown-on-Spey), Dr Alexander James Murray Drennan (Edinburgh) and Dr Wm. Forbes (Edinburgh) were elected Fellows of the College.

Royal College of Surgeons of Edinburgh.

AT a meeting of the Royal College of Surgeons of Edinburgh held on 20th July, Professor R. W. Johnstone, President, in the Chair, the following who passed the requisite examinations were admitted Fellows: Denis Charles Bodenham, M.B., CH.B., UNIV. BRISTOL 1939, M.R.C.S.ENG., L.R.C.P.LOND., 1939; Roy Theodore Scovel Goodchild, M.B., B.S. UNIV. LOND. 1930; Thomas Labatt Lawson, M.B., B.CH., B.A.O., Trinity College, Dublin, 1938; Michael Lentin, M.B., CH.B., B.A.O. NAT. UNIV. IRELAND 1937; Michael Joseph Murphy, M.B., B.CH., B.A.O. NAT. UNIV. IRELAND 1939; John Alexander Vere Nicoll, M.R.C.S.ENG., L.R.C.P.LOND. 1935; John Archibald Simpson, M.B., CH.B. UNIV. EDIN. 1942; John David Stenstrom, M.D., C.M. UNIV. M'GILL, CANADA 1938; Kenneth Frank Wilsdon, B.M., B.CH. UNIV. OXFORD 1939.

Higher Dental Diplomates:—The following candidates, having passed the requisite examinations, were admitted Higher Dental Diplomates: Jack Stuart Beresford, L.D.S. UNIV. NEW ZEALAND 1941; Alfred Henry Lemyman, L.D.S., R.C.S.EDIN. 1931; Leslie Bernard Scher, L.D.S. UNIV. CORK 1944; Frederick William Sturgass, L.D.S. UNIV. MANCHESTER 1933.

At a meeting of the Royal College of Surgeons of Edinburgh, held on the 20th July, it was resolved that, to celebrate the victory in Europe, the Honorary Fellowship of the College be conferred upon: Admiral of the Fleet Sir Andrew B. Cunningham, K.T., G.C.B., D.S.O.; Brigadier-General Elliot C. Cutler, United States Army Medical Service; Dr Andrew Davidson, Chief Medical Officer, Department of Health for Scotland; Surgeon-Vice-Admiral Sir Sheldon F. Dudley, K.C.B., F.R.S., D.G.M.S., Royal Navy; Major-General Paul R. Hawley, United States Army Medical Service; Dr Eardley L. Holland, P.R.C.O.G.; Professor Johan Holst, Oslo; Miss Florence Horsbrugh, C.B.E.; Sir Alfred Webb-Johnson, K.C.V.O., C.B.E., D.S.O., P.R.C.S.ENG.; The Rt. Hon. Thomas Johnston, LL.D.; Sir Edward Mellanby, K.C.B., F.R.S.; Air-Marshal Sir Harold E. Whittingham, K.C.B., K.B.E.

Triple Qualification Board.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of L.R.C.P.EDIN., L.R.C.S.EDIN., L.R.F.P. AND S. GLASG.: Norman James Wilson Allan, Ellis Barnett, Bartholomew Oscar Barry, John Archibald William Brown, Patrick Francis Cassidy, Eileen Veronica Abercrombie Clarke, Thomas Davidson Duke, William Wright Fulton, Harry Gardner, Ronald Ruthven Gilfillan, James Joseph Hogan, Evelyn

Mary Lafferty, Brian Lake, Ian Roy Lambah, John Littlejohn, Duncan Livingstone, Ian Mackenzie, Bal Gobin Madhoo, Victor St John de Courcey Magian, Sydney Howard Manners, Alexander Mather, William Semple Millar, Arthur Douglas Moffat, Joseph Anthony Narcisse, Eben Russell Macmillan Nicol, Stanley Pearson, William Ross Sadler, Phillip Seltzer, George Verghese, Margaret Wilson Macgregor Young; and the following graduate of a recognised foreign University was also admitted a Licentiate, Arnold Heymann, M.D. UNIV. WURZBURG.

NEW BOOKS

Cleft Palate and Speech. By MURIEL E. MORLEY, B.SC., F.C.S.T. Pp. xii+160, with 52 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 7s. 6d. net.

THIS little volume by an experienced speech therapist is full of valuable information. Miss Morley describes fully the anatomy and physiology of the affected area, with special reference to the importance of the palato-pharyngeal sphincter, pointing out that the final result of a cleft palate operation depends on the efficient function of the sphincteric mechanism; even where surgical repair has not been entirely adequate, normal speech may yet be attained by careful training.

A very detailed description of Wardill's operation is given, too technical perhaps for the therapist, followed by a full account of the speech training necessary as an adjunct in the majority of cleft palate cases. The book ends with an instructive series of actual patients illustrating the many problems that the therapist may have to face, and this volume should prove of great value to those for whom it is written.

Trauma in Internal Diseases. By RUDOLPH A. STERN, M.D. Pp. xxiv+575. New York: Grune & Stratton. 1945. Price $6.75.

Disease starts spontaneously or as the result of infection or of a degenerative change. When trauma precedes, then considerable doubt is raised in the medical man's mind as to the exact relation between the trauma and the onset of the disease. The layman, not having the informed knowledge of pathology, summarily correlates the trauma with the onset of the disease. While trauma may not be the cause of a diseased process, it may precipitate its onset or accelerate its course, and thus it becomes an ætiological factor in that case.

The author of this volume is a physician of considerable experience in traumatic diseases and in court practice, so writes with authority. Many case records are apt to be a weariness to the reader, but Dr Stern discusses them so skilfully that he maintains interest to the end. It is a book well worth reading and especially by those who have to give an opinion on the knotty problem of trauma and the onset of a disease.

The Essentials of Chiropody. By C. A. PRATT, Member of the Chartered Society of Physiotherapy. Pp. xii+156, with 34 illustrations. London: H. K. Lewis & Co. Ltd. 1945. Price 10s. net.

Chiropody is a branch of treatment much neglected by the medical profession, and this book, which admittedly has been written for beginners, is one which should claim the doctor's attention. It begins with a short account of the anatomy of the foot and leg, then goes on to discuss foot hygiene and the principles of treatment. Consideration is then given to various common ailments and the method of dealing with them. The book is well written and gives a short but clear account of the various disorders. It is one which should be in the hands of every general practitioner.

NEW EDITIONS

Hygiene. By J. R. CURRIE and A. G. MEARNS. Second Edition. Pp. xvi+432, with 89 figures, 13 in colour. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 21s. net.

Currie's manual of public health has Dr A. G. Mearns' name on the title page of the second edition. It was originally written for students of medicine and general practitioners, but is now enlarged to serve also those engaged in the various branches of public health.

The ground covered is extensive, including all branches of public health, industrial hygiene and social welfare work, with community diseases and parasitology. There is an interesting chapter on inheritance, and a postscript on post-war planning.

The book is written in a clear and interesting fashion, and is well illustrated. Those requiring a comprehensive survey of public health work, not overburdened with detail, will find it very useful.

A Text-book of Psychiatry. By D. K. HENDERSON, M.D., F.R.C.P.ED., and R. D. GILLESPIE, M.D., F.R.C.P., D.P.M. Sixth Edition. Pp. xii+719. London: Oxford University Press. 1944. Price 25s. net.

The remarkable progress in psychiatry that has been made in recent years has necessitated considerable rearrangement and modification of the text in the present edition. Much more emphasis has been given to the social aspects of psychiatry, which are likely to receive even more attention in the near future. The authors take a wide view of their responsibilities, and have endeavoured to keep their subject in close touch with the manifold problems of the consulting room, the home, the school, the work-place, the hospital and human life in general.

Synopsis of Medicine. By Sir HENRY TIDY. Eighth Edition. Pp. xx+1215. Bristol: John Wright & Sons Ltd. 1945. Price 30s.

The eighth edition of this well-known book has been considerably revised, and much has been added concerning recent advances in treatment. The Rh factor in its relation to the hæmolytic anæmias of the newborn and the use of vitamin K in prothrombin deficiencies have been fully discussed. A most useful article on the sex hormones and their value in treatment has also been added. The treatment of malaria has been completely rewritten, and includes the Army standard recommendations. Excellent concise accounts of more newly recognised diseases, including sarcoidosis, primary atypical pneumonia and the crush syndrome, have been added, and many other articles have been extensively rewritten. In all sections this book has been brought up to date with current medicine and should be of great value.

BOOKS RECEIVED

EAGER, RICHARD, O.B.E., M.D., CH.B. The treatment of Mental Disorders. (*W. V. Cole & Sons, Exeter*) 7s. 6d. net.

Compiled by JOHN F. FULTON, PHEBE M. HOFF and HENRIETTA T. PERKINS. A Bibliography of Visual Literature, 1939-1944. (*Charles C. Thomas, Ill., U.S.A.*) $3.00

KEYS, THOMAS E. The History of Surgical Anæsthesia. (*Schuman's, New York*) $6.00

MCCORMICK, CHARLES O., A.B., M.D., F.A.C.S. A Textbook of Pathology of Labour, the Puerperium and the Newborn (*Henry Kimpton, London*) 37s. 6d. net.

MAXWELL, JAMES, M.D., F.R.C.P. Introduction to Diseases of the Chest. Second Edition . . . (*Hodder & Stoughton Ltd., London*) 12s. 6d. net.

BOURNE, ALECK W., M.A., M.B., B.CH., F.R.C.S., F.R.C.O.G., and LESLIE H. WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G. Recent Advances in Obstetrics and Gynæcology. Sixth Edition (*J. & A. Churchill Ltd., London*) 18s.

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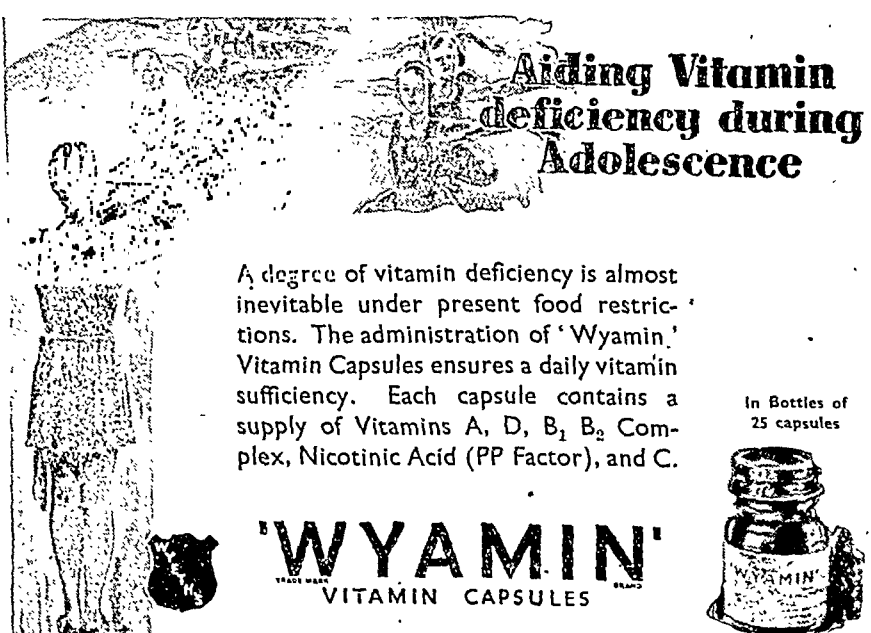

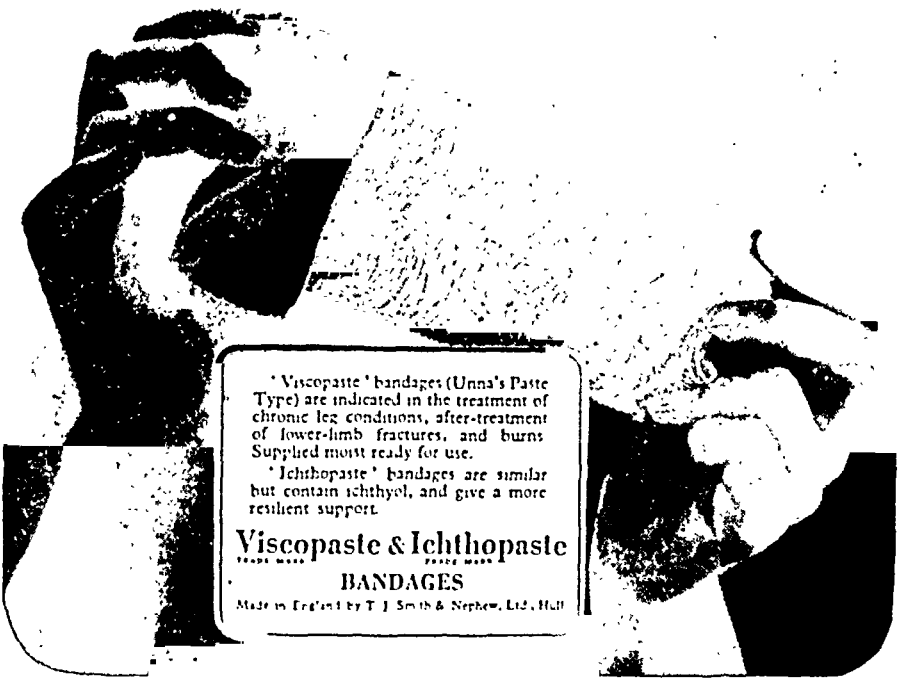

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Edinburgh Medical Journal

October 1945

THE FUTURE OF POST-GRADUATE EDUCATION IN EDINBURGH

By L. S. P. DAVIDSON

THE problem with which I wish to deal is that of Post-graduate Education, a subject of paramount importance to the future welfare of Edinburgh as a centre of medical education. As you are aware, all medical officers in His Majesty's Forces have been informed by the Government that on demobilisation they are entitled to ask for and receive post-graduate education, which will vary according to the specification of the demobilised officer. During his period of post-graduate training he is to receive certain emoluments under the headings of pay and maintenance allowances. The Government have placed the onus of providing this training and carrying out these financial obligations on the Universities of Great Britain. It is estimated that more than 1000 Edinburgh medical graduates have joined the Forces during the past six years. Large numbers will demand that their Alma Mater shall fulfil her obligations to them by providing suitable post-graduate training to fit them for their rôle of general practitioners or specialists in the new comprehensive medical service which will shortly come to fruition. We are in honour bound to do all in our power to meet the legitimate demands of our graduates who have served for years with great distinction in our armed forces in every quarter of the globe. Nor must it be thought that with the completion of demobilisation our responsibility for providing post-graduate education will cease. On the contrary, it is certain that in the future post-graduate training must be provided for every general practitioner at periodic intervals throughout his professional career, as it is only by such means that the practitioner can keep in step with the advances in knowledge which follow each other at such frequent intervals at the present time. Furthermore, the need for a great increase in the number of all types of medical and surgical specialists for the new comprehensive Health Service can only be met if adequate post-graduate training facilities are provided. Lastly, we may expect a great influx to Great Britain of medical graduates from the Dominions and Colonies whose Governments are preparing schemes whereby selected candidates will be given financial aid to enable them to return to the Mother Country in order to obtain the higher diplomas in

Medicine and Surgery. I have recently discussed these matters with the heads of the Medical Services of Canada, Australia, New Zealand and India, and it is certain that if proper facilities are available for post-graduate training a veritable medical invasion of Great Britain may be expected to begin within two years of the completion of the war. The information which I have received makes it abundantly clear that we would be most unwise to rely unduly on the sentimental and historical background of the Scottish capital or on Edinburgh University's past record as a great centre of learning to attract our quota of post-graduate students from overseas. Such sentimental reasons will undoubtedly turn the eyes of many post-graduate students towards Edinburgh, but their selection of a post-graduate centre will ultimately be based essentially on the quality of the instruction given and the clinical and laboratory facilities available for post-graduate training. While every University with a medical school will take part in the provision of post-graduate training for demobilised medical officers, many will discontinue serious post-graduate education when the post-war emergency is over. Some centres, however, must continue this important work, and we can rely with certainty on a great expansion of activity in this direction at the Empire post-graduate school in London and at the ancient residential Universities of Oxford and Cambridge. In addition, certain other of the more progressive universities will wish to stake a claim in this field, and one of these will assuredly be the great University of Edinburgh. We cannot countenance, and we dare not contemplate, even the thought of failure on our part to secure a prominent place in the great new world of post-graduate education which is now unfolding itself. The effect of such a failure on the reputation of our Royal Colleges and on the value of their higher diplomas would be disastrous, while the future well-being of our famous University School for training undergraduates would be seriously impaired. No problem at the present time surpasses in importance this issue of providing in Edinburgh post-graduate facilities of the highest quality, and in adequate amounts, to meet the demands which may be expected in the near future. The bringing to fruition of such a scheme must be the ardent desire of everyone who has the interests of the Edinburgh Medical School at heart. Accordingly, I propose to place before you my personal views on certain requirements for post-graduate education which must be secured, developed and integrated if success is to be achieved.

It has been the custom in recent times for leading political figures to declare their future policies in terms of plans lasting for three or five years, and to subdivide their programme into points or headings. This method has the merit of enabling the average hard-pressed citizen to visualise the salient features of the plan freed from a mass of detail which tends to obscure the essential objectives. The plan for post-graduate training which I now put before you I shall call a two years' plan, because I believe that by the end of that period we can and must be prepared to accept large numbers of post-graduate

students from all parts of the world who wish to train as medical and surgical specialists. I believe that it should be possible in two years to complete the reconstruction of buildings required for clinical instruction, systematic teaching and laboratory work; to collect and train the required numbers of instructors; and to work out the schedule of training best suited to the different categories of post-graduate students whom we may expect.

I now submit for your consideration a five-point programme which covers the essential requirements for the formation of a successful post-graduate school in Edinburgh.

(1) There must always be a close and friendly co-operation in Edinburgh between the University and the two Royal Corporations. In recent times this friendly relationship has been somewhat disturbed by the existing diversity of opinion on whether the University should be the sole body to conduct undergraduate medical education. Into this vexed question I do not propose to enter. On the question of post-graduate education, however, in which instruction in the clinical subjects occupies such a prominent place, I have no hesitation in stating that the Royal Colleges have not only the right but the duty of taking a leading part in formulating and carrying out schemes in this field. Although the Government placed the responsibility for post-graduate education on the University of Edinburgh, it was a wise and proper step for the University to invite the co-operation and help of the Royal Colleges. A combined Post-graduate Board has now been set up, and this constitutes the first essential step for the successful formation of a post-graduate centre. Success may ultimately depend more on the quality of the individual members of this Board than on any material aspects such as hospital buildings or laboratories. The selection of each member must be made with the greatest care, and preference should be given to men who have proved their worth as teachers and administrators and who are known to have a deep and burning interest in medical education. There must be ample representation of young men in the prime of life who retain their physical vigour and capacity for visualising future requirements. In the near future we can confidently expect the return from the Forces of medical and surgical specialists who have established a great reputation in all parts of the world, and these men must occupy an important rôle in post-graduate education. If the Board is to fulfil its important duties, each member must be prepared to give up much of his time and thought to post-graduate problems. He must be prepared to travel widely to gain first-hand knowledge of how training is being conducted both at centres in this country and overseas. He must be prepared to allow his favourite assistant to be seconded to post-graduate teaching if he is selected for this post, even if this entails much inconvenience. He must use his influence to direct clinical material from his own wards to the post-graduate hospital, or to another clinic in his own hospital, if by this means post-graduate training is helped.

In conclusion, I would once again say that the successful creation

of Edinburgh as a post-graduate centre will depend more on the quality, composition, and determination of the Post-graduate Board than on any other single factor.

(2) A post-graduate hospital must be created in which no undergraduate instruction is given. It is widely agreed that post-graduate and undergraduate teaching should as far as possible be undertaken in different institutions, and never at the same time and in the same wards in which instruction for medical students is proceeding. While the basic training in medicine and surgery should be carried out in a specially selected institution, instruction in the special subjects must be given to post-graduate students at the appropriate hospitals or in the special departments of hospitals used for the teaching of undergraduates. To obviate the simultaneous mixture of undergraduate and post-graduate students at classes, special arrangements must be made with the Boards of Management of the hospitals concerned to permit post-graduate teaching in the afternoons, especially on out-patients who have been carefully selected for the purpose of illustrating particular clinical problems. Individual post-graduates on the completion of their basic training could with advantage to all concerned be attached as clinical assistants to heads of the clinical units in the teaching hospital of the area. In the past post-graduate instruction in Edinburgh was mainly carried out in the Royal Infirmary in wards already overcrowded with medical students and by physicians and surgeons already overburdened with hospital and private practice and undergraduate teaching. Some of the teaching was brilliant, much was moderate in quality and some was definitely bad. If we are to receive Government support for post-graduate teaching in Edinburgh in the years to come, and if we are to attract our quota of post-graduates, we must aim at something infinitely better than that accomplished in the past. Those who are satisfied with our past efforts must be out of touch with the standards set by the leading American medical schools or are looking at the past through rose-coloured glasses. Post-graduate instruction is such an important matter that those taking part in it must have ample time to give it the attention which its importance merits. Hence it is essential that a body of teachers selected for their professional skill and capacity to teach must be seconded for post-graduate teaching and be relieved of all duties concerned with undergraduate instruction. We must be prepared to send to the post-graduate hospital only the best of our teachers, and we must be prepared to accept ungrudgingly the handicaps which such a loss may impose on our work in hospital or at the University. Adequate payment for post-graduate teachers according to the amount of time given to teaching is of course essential, and for this purpose we can expect help from the University Grants Committee. The first step has already been made for the provision of a post-graduate hospital in Edinburgh, and the approaches made by the Post-graduate Board have been very favourably received by the Board of Management of the hospital concerned. This enlightened Board fully appreciates

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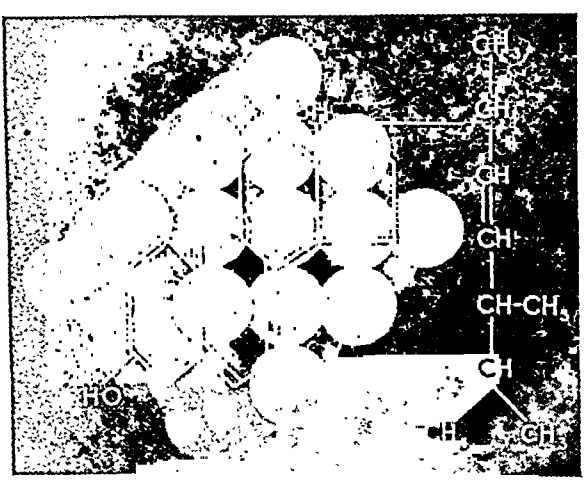

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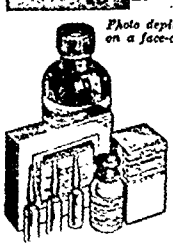

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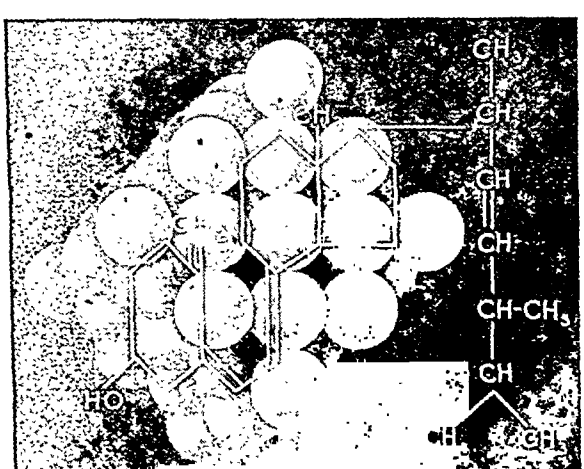

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the benefits which their patients will receive from having on the staff of the hospital instructors selected because of their high professional skill. Much, however, requires to be done in improving laboratory and teaching facilities. I have no hesitation in prophesying a great future for this enterprise if the friendly relations already established between the bodies concerned are continued into the future, and if we all support this project with every means at our disposal.

(3) It is now widely agreed that special instruction in the basic sciences of Anatomy, Physiology, Biochemistry and Pathology constitutes an essential part of the teaching of would-be medical and surgical specialists. The Royal College of Surgeons of England has long accepted this principle, and has made it compulsory for candidates for the Fellowship to pass a special examination in Anatomy and Physiology. It seems certain that Edinburgh must follow suit, not only because of the correctness of the principle involved, but because the failure to institute such an examination may be reflected in their diploma not being recognised in our Dominions overseas. In my experience the majority of candidates for the examination for the membership of the College of Physicians are lamentably ignorant of these basal sciences, and I feel most strongly that they should be incorporated as an integral part of the examination. If, however, we are to demand an adequate knowledge of these sciences, we must be prepared to supply instruction in them up to the standard required for our higher diplomas. For this purpose we require classrooms, laboratories, museums and libraries. Since no accommodation is available in the University for these purposes, and since we may dismiss the possibility of constructing the necessary accommodation for many years to come because of the priority placed on the building of dwelling-houses, there appears to me only one site at which this all-important work can be done in the immediate future, namely in the classrooms and laboratories at Surgeons' Hall. These could be altered and brought up to standard at moderate cost if the authorities controlling Surgeons' Hall so desired. I am convinced that if the Royal Corporations in Edinburgh wholeheartedly devoted their energies, experience, premises and funds solely to the advancement of post-graduate education, their reputation and financial stability would advance to levels undreamed of in the past. Believing as I do that adequate experience in the basal sciences constitutes an essential part of post-graduate training, I would earnestly ask the Councils of the Royal Colleges to give this problem the serious consideration which it merits.

(4) A residential hall or club must be provided for our post-graduate students, particularly for those from overseas, if they are to derive the full benefit of their sojourn in our midst. A comfortable well-furnished residence at which some could reside and many could dine and discuss the day's work and other matters of local and general interest would play an important part in promoting the comfort and happiness of the students. Provision for social contacts under pleasant

surroundings between fellow-students from different countries and between students and teachers constitutes an essential feature of any post-graduate scheme. In the past we have been content to allow our post-graduate students to languish in bed sitting-rooms scattered throughout the city and to return home equipped with some higher technical qualification, but lacking an acquaintance with Scottish hospitality, traditions and culture. The importance of this aspect of post-graduate education has been recognised at the Rowett Institute in Aberdeen where, as a result of the vision and enthusiasm of Sir John Orr, a large sum of money was collected to build and equip Strathcona House as a residence for post-graduate students studying animal nutrition. On a recent visit to London I had the good fortune to be shown over an institution situated in the heart of the Metropolis which reminded me of my student days at Cambridge. This residence is called London House, and is a home from home for students from overseas who come to London for post-graduate training. Our neglect in the past to visualise the essential needs of a post-graduate centre cannot be tolerated in the future if we are to gain our place in this educational field. Accordingly I suggest that the bodies responsible for post-graduate education in Edinburgh should jointly buy or construct a residential hall which might be called Edinburgh House. I understand that Ramsay Lodge, long used as an undergraduate residence, is on the market and can be purchased at a low cost, and I would suggest that the acquisition of the property as a post-graduate residence is worthy of immediate consideration. The University of Edinburgh and the Royal Corporations are wealthy bodies which could jointly undertake this commitment without affecting to any material degree their financial stability. Only if we can show that we are prepared to put wholeheartedly our time, our labour, and our funds into the promotion of schemes for post-graduate education can we expect, or do we deserve, to get additional help from Government sources, from charitable foundations such as the Nuffield Trust and from private benefactors.

(5) The time has come when it is imperative to create a Royal College of Physicians and a Royal College of Surgeons of Scotland. In passing, it is of interest to recall that the Royal Warrant issued in 1861 granting a renewal of the Charter of the Royal College of Physicians of Edinburgh, gave the College permission to use the title of Royal College of Physicians of Scotland. For reasons best known to itself the Council of the College of that day decided not to accept this privilege. There are at least three important reasons why this step is urgently required. First, some central authoritative body is needed to represent the interests of all medical and surgical specialists resident in Scotland. With the introduction in the near future of the new comprehensive Health Services, the Secretary of State for Scotland will require advice on problems connected with the specialist services, and this he can only satisfactorily obtain from a national body. Representations made on behalf of specialists practising in Scotland by a

national body would carry much greater weight in Government circles than those coming from corporations or organisations of local origin. Second, the great increase in Fellows on the roll of attendance would be an invaluable acquisition for the supply of teachers and examiners for the post-graduate students whom we hope and expect to attract in large numbers. Third, the enhanced prestige which a national body would have in the eyes of the medical profession at home and abroad must be apparent to everyone, and its post-graduate diploma would command a corresponding increased value to prospective post-graduate candidates. We should remember that the Royal Colleges of Edinburgh are competing against the National Corporations of England, Ireland, Australasia and Canada. Individually and collectively we must ever be on our guard against falling into the besetting sin of attributing an exaggerated importance to the influences which we exert on national and international medical problems and policies. If the desirability of creating national corporations of medicine and surgery in Scotland is accepted, a decision must be reached on the most suitable place where they should be located. To an unbiased observer the question presents no difficulty, since Edinburgh as the capital city of Scotland and the seat of government is the obvious site for the newly created national corporations. In addition, no other city in Scotland possesses medical premises, libraries or museums comparable in size or quality to those at present available in Edinburgh. When the national colleges have been created, their fellowships should be offered to all fellows of the Royal Corporations of England, Edinburgh and Glasgow who are resident in Scotland. Thereafter admission should be made through the customary channels of examination and election. Conversations which I have had with leading medical specialists from the West, North and East of Scotland convince me that this project will receive wide support in enlightened medical circles. The advantages which will accrue to the majority of physicians and surgeons and to post-graduate education in Scotland will far transcend any loss of prestige or influence enjoyed at present by local or sectional interests.

I submit that these proposals constitute not a nebulous ideal but a practical plan which can be put into operation within two years if they receive the active support of all medical men who have a burning desire to promote the future welfare of Edinburgh as a great centre of medical education. I would especially appeal for their most careful consideration by our graduates at present in the Services on whose shoulders will largely fall in the future the responsibility for organising and carrying out post-graduate education in Edinburgh. I know that I can count on the support of those who have received their degrees at this great ceremony because of the obvious benefits which will accrue to them on their return from the Forces.

NUCLEOPROTEINS IN GROWTH AND DEVELOPMENT *

By J. NORMAN DAVIDSON, M.D., D.Sc., F.R.S.E.

Physiology Department, The University of Aberdeen

THE nucleoproteins form a group of substances which have recently come into prominence on account of their rather unusual properties and remarkable biological activity. They consist of protein associated with nucleic acids, complex organic compounds which have been rather unfortunately named, since in many cells there is more nucleic acid outside the nucleus than inside it.

Before considering the function and biological activity, pathological as well as physiological, of these substances, we must first take a brief survey of their rather complicated structure.

It has been known for a long time that two main types of nucleic acid exist. One type was originally obtained by Miescher from the nuclei of pus cells, from salmon sperm and from the thymus gland, and is usually known as *deoxyribonucleic acid* or *thymonucleic acid* (*animal nucleic acid*, *chromonucleic acid*). It is found exclusively in the cell nucleus.

The other type of nucleic acid was originally discovered in yeast, and is usually known as *ribonucleic acid* or *yeast nucleic acid* (*pentose nucleic acid*, *plasmonucleic acid*, *zymonucleic acid*, *phytonucleic acid*). It is found in the cell cytoplasm, and some observers maintain that small amounts occur in the nucleus also.

Ribonucleic acid, but not deoxyribonucleic acid, can be attacked and broken down by an enzyme *ribonuclease* which has the rather unusual property of being very stable to heat. This enzyme therefore affords one means of distinguishing between the two types of nucleic acid.

The two acids differ slightly in the products of their hydrolysis. When ribonucleic acid is broken down the products are the purine bases adenine and guanine, the pyrimidine bases cytosine and thymine, the pentose sugar *d*-ribose and phosphoric acid. Deoxyribonucleic acid under the same conditions yields adenine and guanine, cytosine and thymine, the sugar 2-deoxyribose, and phosphoric acid. The main difference between the two types of acid, therefore, is that deoxyribonucleic acid contains deoxyribose and the methylated base thymine (methyl uracil) in place of the ribose and uracil found in ribonucleic acid.

To build up the nucleic acid molecule these individual units must be condensed together with elimination of water. A molecule of a

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, Edinburgh, on 2nd August 1945.

purine or a pyrimidine base can condense with a molecule of pentose to form a nucleoside. When a nucleoside molecule is condensed with phosphoric acid the product is termed a *nucleotide* (*mononucleotide*). Four such mononucleotides each containing a different base can condense together to form a *tetranucleotide*, which is the unit out of which the nucleic acids or polynucleotides are built by a process of polymerisation (Table I).

TABLE I

Purine or pyrimidine BASE+SUGAR⟶NUCLEOSIDE

Purine or pyrimidine BASE+SUGAR+PHOSPHORIC ACID⟶NUCLEOTIDE

Four different NUCLEOTIDES⟶TETRANUCLEOTIDE

polymerisation ↓

POLYNUCLEOTIDE } NUCLEIC ACID

↓ +PROTEIN

NUCLEOPROTEIN

↓ +PHOSPHOLIPIN

PHOSPHOLIPIN-NUCLEOPROTEIN COMPLEX

In the living cell, however, nucleic acids probably do not exist in the free state but are found in combination with protein as *nucleoproteins*. In the nucleus the deoxyribonucleic acid is combined with the basic proteins, the protamines and histones. In the cytoplasm the ribonucleic acid is combined with protein components about which we know very little to form the *ribonucleoproteins*. They in their turn may be associated with phospholipins in the form of *phospholipin-ribonucleoprotein complexes*.

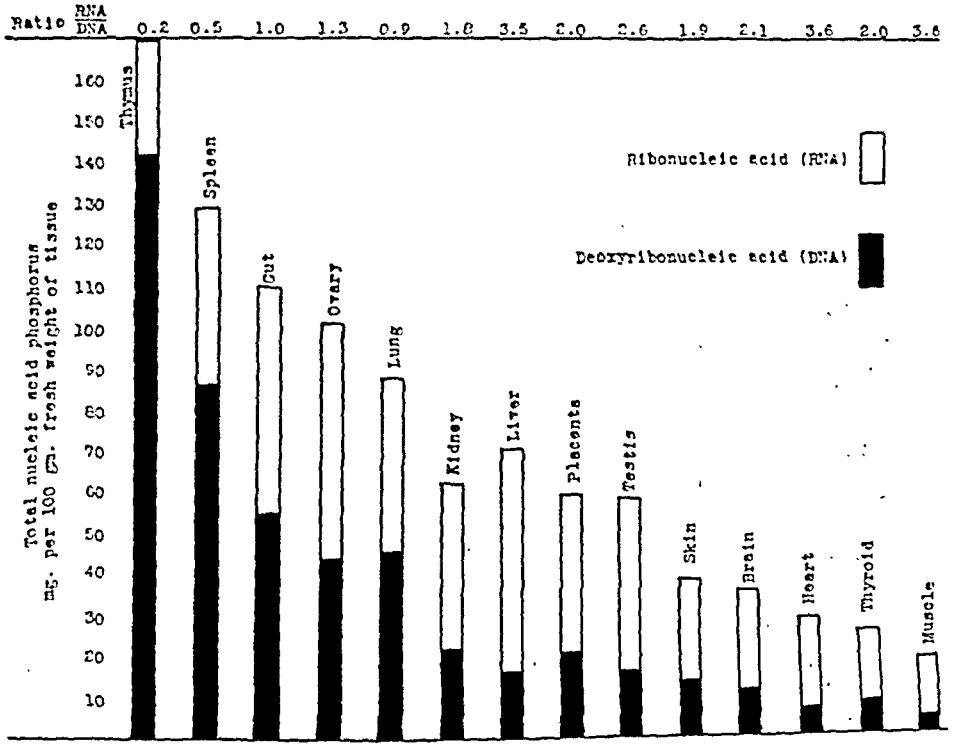
Deoxyribonucleic acid was originally obtained from animal cells and ribonucleic acid from yeast cells or plant tissues, and for a time it was thought that the former was characteristic of the animal kingdom and the latter of the plant kingdom, but it eventually became apparent that this view was untenable. Deoxyribonucleic acid was demonstrated in plant cells, and evidence gradually accumulated suggesting that ribonucleic acid or its nucleotides were present in animal tissues. This was conclusively proved twenty years ago when Jorpes in Sweden prepared a ribonucleic acid from the pancreas. Since then ribonucleic acids have also been isolated from liver, intestine, and kidney and they appear to be widespread in animal tissues. Indeed, in many tissues the amount of ribonucleic acid exceeds the amount of deoxyribonucleic acid (Davidson and Waymouth, 1944 *a* and *c*) (Fig.). The whole human body, for example, contains approximately 90 grams of ribonucleic acid and approximately 30 grams of deoxyribonucleic acid.

It is of some interest, therefore, to examine the localisation and distribution of the two types of nucleic acid in the individual cell, and to try to discover what functions they serve. For these purposes rather specialised methods have had to be employed.

It is of course possible to separate the cell nucleus from the

cytoplasm and to examine each separately, but such methods are usually elaborate and tedious. For example, one can suspend dried and powdered tissue in columns of organic solvents of graded density so that the nuclei settle out more rapidly than the cytoplasmic fragments. Or one can treat a finely divided tissue suspension with citric acid, when the nuclei can be obtained as a separate layer on centrifuging.

These methods are relatively crude, but the information obtained by their use may be reinforced by the results of histochemical tests of which the best known is probably the so-called Feulgen reaction.



Nucleic Acid Content of Individual Tissues.

This test depends on the fact that when tissue sections are treated with warm dilute hydrochloric acid, the deoxyribonucleic acid is hydrolysed, liberating substances which are able to restore the colour to fuchsin solutions which have been decolourised by sulphur dioxide. Sections treated by the Feulgen technique, therefore, show deep purple staining where deoxyribonucleic acid is found; that is, in the nuclei. Recent work (Stedman, 1943, 1944; Carr, 1945) has cast doubt on the validity of the usual interpretation of the test, but the test still retains some of its usefulness provided that its limitations are recognised (Stowell, 1945).

A second method has been developed by Caspersson (1936, 1940), who has made use of the fact that the pyrimidine and purine bases of the nucleic acids absorb ultraviolet light strongly at a wavelength

of 260 mμ. By using the quartz microscope and measuring the intensity of absorption of ultraviolet light at this wavelength, by tissue sections, or even by portions of individual cells, he has been able to estimate quantitatively the concentration of nucleic acid in various regions of a single cell in amounts as small as 10^{-11} mg. It must be emphasised that this method does not distinguish between the two types of nucleic acid; it simply indicates the presence of strongly absorbing materials, presumably purines or pyrimidines, which may be present in the free state or combined as nucleosides, nucleotides or nucleic acids of either type; but it has usually been assumed that the presence of such highly absorbing materials in regions of the cell which do not give a positive Feulgen test indicates ribonucleic acid. In some cases such a conclusion may be supported by estimations of pentose or of phosphorus.

The third technique also involves the use of tissue sections. In many cells the cytoplasm contains large amounts of chromophilic material which stains deeply with dyes such as toluidine blue or the pyronine of Unna's pyronine-methyl green stain. Whereas the chromatin of the nucleus is Feulgen-positive and consists mainly of deoxyribonucleo protein, the chromophilic material of the cytoplasm is Feulgen-negative. Its chemical nature can be determined by a histochemical test first described by Brachet (1939, 1940, 1941, 1944), who showed that the cytoplasm no longer takes up such stains as pyronine or toluidine blue in sections which have been incubated with the enzyme ribonuclease. The chromophilic material of the cytoplasm would appear therefore to be ribonucleic acid (Davidson and Waymouth, 1944*d*).

This test depends of course on the specificity of ribonuclease for ribonucleic acid. The enzyme is known not to attack deoxyribonucleic acid, but there is some evidence that it may have an influence on other cellular materials such as histones (Cohen, 1945) and the results of the Brachet test should be interpreted with caution. At the same time it should be emphasised that there is very striking agreement between the results and conclusions of Brachet and those of Caspersson, although the two authors have used totally different methods.

By means of these three tests, the Feulgen test, ultraviolet absorption and the Brachet test, the two types of nucleic acid can be localised in the cell. In the first place it can be shown that deoxyribonucleic acid is found exclusively in the nucleus while ribonucleic acid, on the other hand, occurs in the cytoplasm, and is especially abundant in cells with strongly basophilic cytoplasm.

But there is some evidence that ribonucleic acid may also be found in small amounts in the nucleus, chiefly in the nucleolus. The nucleolus contains Feulgen-negative material which absorbs ultraviolet light strongly at 260 mμ and stains with pyronine or toluidine blue. In the cells of sections which have been treated with ribonuclease the ultraviolet absorption of the nucleolus is diminished, and so is its

affinity for basic dyes. The nucleolus also gives positive histochemical tests for pentoses. There is fairly good evidence, then, that in some cells at least the nucleolus contains ribonucleic acid (Caspersson and Schultz, 1940; Gersh, 1943; Mitchell, 1942, 1944; Brachet, 1941*b*).

Such is the distribution of the nucleic acids in the cell. What are their functions?

The chemical aspects of the cell nucleus have been fully discussed recently by Stedman (1944), and it will suffice at this stage to state that, in the nucleus, the deoxyribonucleic acid with accompanying histones and the protein chromosomin is intimately connected with the process of mitotic division. The activity of this nucleic acid in other biological processes may, however, be illustrated by two examples. It has been claimed recently that crude deoxyribonucleoprotein or chromatin prepared from the nuclei of liver cells has the property of stimulating tissue growth and of promoting the healing of wounds (Marshak and Walker, 1944). This observation has still to be followed up and confirmed.

In the field of bacteriology it has been shown that a highly polymerised form of deoxyribonucleic acid which can be obtained from Type III Pneumococci has the property of inducing the transformation Pneumococcus Type II (the unencapsulated R variant) into the fully encapsulated Type III (Avery, MacLeod, and McCarty, 1944).

Our main interest, however, lies not in the nucleus, and its deoxyribonucleic acid, but in the cytoplasm and its ribonucleoproteins. What are the functions of these ribonucleoproteins?

In the first place, they play a part as actual structural units of the cell. In the cell cytoplasm the ribonucleoproteins occur for the main part in the form of phospholipin-ribonucleoprotein complexes which are present in the form of granules or particles. These particles are of two types—large and small.

The large particles are about 0·5 to 2·0 μ diameter and can easily be seen under the microscope. The mitochondria belong to this group and so do the secretory granules or zymogen granules described by Claude (1943 *a* and *b*) in liver and pancreas. But the cell cytoplasm contains, in addition, much smaller particles which are ultra-microscopic in nature, being 50-200 mμ in diameter. In the living cell they can be seen in the dark field microscope as highly refringent small bodies in continuous Brownian movement. They form the chromophilic ground substance of the cytoplasm and may constitute 10-15 per cent., or even as much as 25 per cent., of the dry substance of the cell (Claude, 1943 *a* and *b*). These submicroscopic particles have been termed "microsomes" by Claude (1943*a*).

The presence of both large and small particles can be conveniently demonstrated by submitting small fragments of fresh liver tissue to high speed centrifugation (Brachet, 1941*b*; Jeener and Brachet, 1941; Claude, 1943*b*). When the cells are fixed and stained four separate layers can be identified. The lowest layer (near the centrifugal pole of

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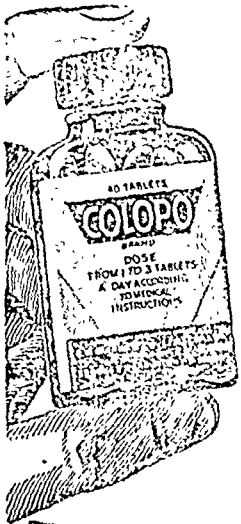

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the cell) represents unstained glycogen which is known to occur in the liver in particulate, and therefore sedimentable, form (Lazarow, 1942). The second layer contains the nucleus and the large particles. Above it is a layer of stainable material showing no definite structure and corresponding to the small particles or chromophilic ground substance which can be distinguished from the fourth or top layer of very lightly staining true hyaloplasm (Claude, 1943*b*).

By a process of differential centrifugation (1500-20,000 × *g*) which has been developed largely by Claude (1943 *a* and *b*), both types of particle can be separated from the cell and can be submitted to chemical analysis (Bensley, 1942; Claude, 1943 *a* and *b*, 1944).

Both types have been shown to contain ribonucleoprotein (Claude, 1943*a*) associated with lipid material some two-thirds of which is phospholipin. Indeed, nearly all the phospholipin of the cell cytoplasm is present in the particles; the interparticulate fluid contains only a negligible quantity (Bensley, 1943). The total fat content is higher in the small particles than in the large particles (Table II).

TABLE II

Composition of Cytoplasmic Particles containing Ribonucleic Acid

	Author.	Term employed.	Species.	Organ.	Diameter.	N per cent.	P per cent.	Total Fat per cent.
Large Particles	Chargaff (1942)	Mitochondria	Rabbit	Liver	...	10·6-11·4	1·1-1·3	35
	Bensley (1943)	Mitochondria	Guinea-pig	Liver	...	...	...	32-38
	Claude (1943*ab*)	Secretory granules	Guinea-pig and rat	Liver	0·5-2·0 μ	12·0	1·3	20-24
	Claude (1943*ab*)	Zymogen granules	Cattle	Pancreas	0·5-2·0 μ	12·0	1·88	20
	Claude (1944)	Mitochondria	Rat	Leukæmic cell	0·5-1·5 μ	11·3	1·7	27
Small Particles	Claude (1943*ab*)	Microsomes	Guinea-pig and rat	Liver	50-300 mμ	9·0	1·5	40-45
	Claude (1943*ab*)	Microsomes	Cattle	Pancreas	...	...	2·1	...
	Claude (1943*ab*)	Microsomes	Chick	Embryo	...	...	2·1	...
	Claude (1944)	Microsomes	Rat	Leukæmic cell	50-300 mμ	9·4	2·2	37
	Bensley (1943)	Submicroscopic particles	Guinea-pig	Liver	...	...	...	42-51

In the adult cell nearly all the ribonucleic acid of the cytoplasm is present in the particles (Jeener and Brachet, 1941), but in some rapidly growing tissues, such as amphibian eggs in course of development, in chick embryos and in yeast, the particles contain only 20 to 40 per cent. of the total ribonucleic acid of the cytoplasm (Brachet and Chantrenne, 1942). The remainder is present in the "free" form which is not sedimentable in the ultra-centrifuge.

The part played by the particles in the internal economy of the

cell is not yet clear, but in the *liver* cell it would appear that part at least of these phospholipin-ribonucleoprotein complexes is present as storage material. Fasting is accompanied by a loss of stainable material and of mitochondria from the cytoplasm, and by a loss of phospholipin and of total nucleic acid. Of the two kinds of nucleic acid it is the ribonucleic acid which disappears, while the deoxyribonucleic acid content of the liver remains almost constant (Davidson and Waymouth, 1944*b*). A similar loss in ribonucleic acid and in phospholipin results from the feeding of a protein-poor diet (Kosterlitz, 1944), and it seems logical to conclude that some at least of the particulate material in the liver cytoplasm represents storage protein.

The particulate components of the cytoplasm, moreover, are endowed with enzyme activity. Two of the chief enzymes present in the particles are the succinic dehydrogenase and the cytochrome oxidase, both of which play an important part in cellular oxidations. They are both absent from the inter-particulate fluid (Bensley, 1942).

The presence of enzymes in the cytoplasmic particles endows them with biological activity of a high order, and Claude (1943*a*) has suggested that the particles may have the property of self-duplication. Indeed, this property appears to be a feature of compounds of protein and nucleic acid such as the genes, the cytoplasmic particles, and the viruses.

This view has been extended by Brachet (1942, 1944), who points out that the cytoplasmic granules constitute ideal organs for protein synthesis. They contain peptidases and other enzymes which play a part in protein synthesis, and also oxidative enzymes which can provide the energy indispensable for such an endothermic reaction. We shall return to this question of protein synthesis later.

In bacterial structure ribonucleic acids play an interesting part in relation to the Gram stain. It has been shown that the dye-retaining material in Gram-positive organisms is a high molecular complex of magnesium ribonucleate with reduced basic protein. The outer shell of ribonucleate can be removed by warm bile salt solutions, leaving behind intact cells which are Gram-negative. When these Gram-negative bacterial skeletons are coupled with magnesium ribonucleate the affinity for the Gram stain is restored. The outer shell of ribonucleate may also be removed from Gram-positive organisms with the aid of ribonuclease, leaving a Gram-negative skeleton (Henry and Stacey, 1943; Henry, 1944; Bartholomew and Umbreit, 1944).

Apart from their rôle as structural components of the animal cell, or the bacterial cell, ribonucleoproteins may also be endowed with biological activities of various kinds. A case in point is the blood-clotting activity possessed by the *thromboplastic protein* of lung tissue which has recently been isolated as a phospholipin-nucleoprotein complex containing ribonucleic acid. It is rather unstable and readily disintegrates into smaller components, some of which also have high thromboplastic activity (Chargaff, Bendich and Cohen, 1944).

The possibility of the production of active fragments from the large ribonucleoprotein molecule is one of considerable importance. It might, for example, explain the observation that ribonucleoproteins of very varied origin, when implanted into the tissues of the amphibian embryo, are capable of inducing the development of the nervous system at the site of implantation. This effect is thought to be caused by breakdown products formed gradually in the tissues from the implanted ribonucleoproteins, and it is significant that preliminary treatment of the implant with ribonuclease reduces drastically its power of causing neural induction (Brachet, 1943).

It has further been suggested that living cells as a response to injury liberate ribonucleic acid derivatives of the nucleotide type which promote cell proliferation, and these substances are sometimes referred to as " wound hormones," although the evidence for their independent existence is still far from conclusive (Davidson, 1943). But it is known that simple nucleotides can exert a powerful influence on cellular development. It has recently been shown, for example, that mixtures of the four mononucleotides derived from yeast ribonucleic acid by partial hydrolysis, when administered parenterally, can induce a leucocytosis of moderate or even leukæmic proportions, and a reticulosis, plasmacytosis and myeloid changes in the lymphoid tissue (Parsons, 1945). Such mixtures of nucleotides are used therapeutically in the treatment of the agranulocytosis which may follow the use of some of the chemotherapeutic drugs (*cf.* Jackson and Parker, 1935).

One of the most interesting groups of nucleoproteins is formed by the filterable viruses. The plant viruses such as tobacco mosaic virus and ring spot virus are ribonucleoproteins, and of these the tobacco mosaic virus has received most attention. It can be harvested in large amounts from affected tobacco plants, and after purification it has been obtained as a crystalline nucleoprotein from which a ribonucleic acid has been isolated. After repeated recrystallisation the properties of the nucleoprotein and its infectivity are unchanged. Here, then, we have the phenomenon of a ribonucleoprotein which has been highly purified and crystallised but which at the same time can act as an infective agent growing and reproducing itself in the living plant cell of its host. The tobacco mosaic virus nucleoprotein has a very high molecular weight (50,000,000) and its molecules, as seen in electron microscope, are rod-shaped (Stanley, 1943).

The virus reacts with the enzyme ribonuclease. So long as the nucleic acid remains attached to the protein it is not attacked by the enzyme, but enzyme and virus can combine to form a virus-enzyme complex which is inactive as an infective agent. The complex can be easily decomposed and the fully infective virus recovered (Loring, 1942). This phenomenon is of some interest since it provides a clue to a possible line of attack in the chemotherapy of virus diseases.

The plant viruses appear to be simple ribonucleoproteins, but some of the animal viruses are also ribonucleoproteins combined with

phospholipin as phospholipin-ribonucleoprotein complexes. The Rous sarcoma virus of the fowl and the equine encephalomyelitis virus are compounds of this type, but most of the animal viruses which have been purified contain not ribonucleic acid but deoxyribonucleic acid, *e.g.* vaccinia elementary bodies, rabbit papilloma virus, influenza virus (Taylor, 1944) and *Esch. coli bacteriophage* (Table III). Such viruses appear to be phospholipin-deoxyribonucleo protein complexes (*cf.* Beard, 1945).

TABLE III

Composition of Virus Nucleoproteins
(*per cent. dry weight*)

Virus.	Nucleic Acid.	Total Lipin.	Phospholipin.	Carbohydrate.
Tobacco mosaic	5·8 RNA	0	0	2·5
Ring spot	40·0 RNA	0	0	15·18
Rous sarcoma	10·0 RNA	36·5	...	...
Equine encephalomyelitis (Eastern strain)	4·4 RNA	48·5	30·0	3·5
Rabbit papilloma	8·7 DNA	1·5	...	...
Vaccinia	5·0 DNA	5·7	2·2	2·8
Influenza A	1·5 DNA	24·0	11·3	12·5
Influenza B	1·2 DNA	23·0	11·2	13·1

RNA = ribonucleic acid.
DNA = deoxyribonucleic acid.

The virus of psittacosis and the *Esch. coli* bacteriophage also contain deoxyribonucleic acid.

Whereas the plant viruses appear to be simple homogeneous crystallisable nucleoproteins, the animal viruses in the electron microscope show evidence of differentiation in internal structure with an outer shell probably of phospholipin, and they have a chemical composition resembling that of the cytoplasmic particles. Indeed, their relationship to the cytoplasmic particles and the possibility of their origin from the cytoplasmic particles has aroused a good deal of interest and may be of considerable importance (Du Buy and Woods, 1943; Haddow, 1944; Darlington, 1944; Beard, 1945; Potter, 1945).

Finally we might consider very briefly the relationship of the nucleoproteins to the question of tissue growth.

The process by which nucleic acids are built up in the developing eggs or embryos of different species is of some interest. In simple marine forms such as the sea urchin, the total nucleic acid content of the embryo as measured by the nucleic acid phosphorus or the purine content remains constant during development. At the same time the deoxyribonucleic acid content rises while the pentose content, and therefore presumably the ribonucleic acid content, falls. It would appear, therefore, that the nuclear deoxyribonucleic acid is synthesised from the initially abundant store of cytoplasmic ribonucleic acid (Brachet, 1937, 1944).

As we ascend the animal scale this relatively simple relationship no

longer holds. Whereas in the sea-urchin 100 per cent. of the total nucleic acid which is present at the end of embryonic development was originally in the egg at the beginning of the process, in the crab and starfish the figure is 80 per cent. and 61 per cent., and in the chick embryo only 7 per cent. (Brachet, 1944). These species, therefore, must synthesise both types of nucleic acid quite readily. In the embryos of birds and reptiles, and presumably in mammals also, both types of nucleic acid are synthesised on a large scale, but at the same time it is possible that at least part of the nuclear deoxyribonucleic acid is synthesised by way of cytoplasmic ribonucleic acid. In this connection some experiments carried out by Mitchell (1942, 1943, 1944) are worth mentioning. Mitchell took biopsy specimens of human tumours before and after X-ray therapy and examined them by ultraviolet light in the quartz microscope by a technique similar to that of Caspersson. He found that after irradiation the cytoplasm of these rapidly proliferating tumour cells contained large amounts of materials which absorbed ultraviolet light at a wavelength of 260 mμ and which were therefore presumably ribonucleic acids or ribonucleotides. He suggests that these ribonucleotides are formed in the cell cytoplasm from unknown precursors and that they pass into the nucleus where they are reduced to deoxyribonucleotides which are finally built up into deoxyribonucleic acid. Irradiation blocks this process and ribonucleotides accumulate in the cytoplasm.

But apart from these considerations of the biosynthesis of nucleic acids in growing tissues, the ribonucleic acids have recently received attention on account of their occurrence in large amounts in rapidly growing tissues, such as those of the young embryo, and some of the properties of embryonic extracts have been attributed to their presence. For example, it has been known since the early work of Carrel (1912) that cultures of chick fibroblasts may be maintained *in vitro* over a period of many years, and indeed apparently indefinitely, in a medium containing the juice of embryonic tissue, and much speculation has arisen as to the chemical nature of the growth-promoting factors involved (*cf.* Needham, 1942). Fischer has claimed that the growth-promoting activity of embryo juice is associated with a ribonucleoprotein which he has prepared and termed "embryonin," but so far all attempts to purify it have failed (Fischer, 1941; Fischer and Astrup, 1943). Although it has been proved that embryo juice is rich in ribonucleoproteins and that the nucleoprotein fraction may have some growth-stimulating power at low concentrations (Davidson and Waymouth, 1944*a*, 1945), there is still no good evidence that the growth-promoting power of embryo juice can be attributed to this one particular fraction alone.

Nevertheless both this nucleoprotein fraction and whole embryo juice have been used by a number of surgeons to accelerate the healing wounds. This type of therapy has never become very popular in this country, although Russian surgeons have developed it on a fairly

large scale in the treatment of battle casualties, using the embryo juice in the form of an emulsion or ointment (Goldberg, 1944, 1945; Davidson, 1945).

Work of this type has inevitably focussed attention on the rôle of ribonucleic acids in rapidly growing tissues, and the Caspersson school, using the ultraviolet absorption method, found evidence at an early stage for the presence of ribonucleic acids in high concentrations in the cytoplasm of rapidly growing tissues such as developing sea-urchin eggs, the root tips of plants, and the imaginal discs of *Drosophila* larvæ but not in the homologous mature tissues (Caspersson and Schultz, 1939, 1940). Indeed, for a time it appeared that a high concentration of cytoplasmic ribonucleic acid was characteristic of rapidly growing tissues, such as those of embryos or tumours, but evidence has since accumulated to show that ribonucleic acid is a general constituent of adult animal cells, and that although it is present in high concentration in most embryonic tissues, the concentration of deoxyribonucleic acid is high also, so that the ratio of one type of nucleic acid to the other is the same in the embryo as in the corresponding adult tissue (Davidson and Waymouth, 1944*a*). Moreover, ribonucleic acid is abundant in the cytoplasm of the cells of non-growing tissues, *e.g.* in the liver, in the pancreas, and in the Nissl's granules of nerve cells (Brachet, 1944; Caspersson, 1941).

An examination of the ribonucleic acid content of different tissues reveals some rather striking features (Table IV). The figures quoted

TABLE IV

Ribonucleic Acid Phosphorus mg. per 100 grams Fresh Tissue

Pancreas	150
Ovary	57
Liver	55
Gut	55
Spleen	43
Lung	42
Testis	42
Kidney	41
Placenta	39
Thymus	28
Skin	25
Brain	24
Heart	23
Thyroid	16
Muscle	15

here are based on actual nucleic acid estimations, but they agree very well with the results obtained by Brachet (1941 *a* and *b*) by two different methods: (1) pentose estimations on the fresh tissue and (2) assessments of the relative nucleic acid content of tissues based on the Brachet histochemical test.

Ribonucleic acid is present in small amounts only in muscle, heart, brain, and in most endocrine glands including the thyroid, but it is abundant in exocrine glands, such as the pancreas, and in the gastric and intestinal mucosa. In the hæmopoietic system ribonucleic acid

is most abundant in young cells, *e.g.* lymphoblasts, and disappears progressively during maturation (Brachet, 1941*b*). Ribonucleic acid is abundant in the Malpighian layer of the skin, in oocytes in course of vitellogenesis, in the cells of regenerating limb buds (Jakovleva, 1943; Brachet, 1944), and, in general, in tissues where mitotic division is active—for example, embryonic tissues, hair follicles, imaginal discs of insects, etc.

All cells or tissues containing a high concentration of ribonucleic acid have one feature in common—they are all the seat of intense protein synthesis, either for purposes of secretion as in the pancreas, or for purposes of cell multiplication, as in the basal layers of the skin. The liver, which synthesises a large part of the plasma protein, has a high ribonucleic acid content. Ribonucleic acid is also abundant in viruses, yeasts and bacteria, all of which are capable of intense multiplication.

We see, then, that a high concentration of cytoplasmic ribonucleic acid is characteristic of cells in which protein synthesis is vigorous. It is now possible for us to obtain an inkling as to the part played by the ribonucleoproteins in protein synthesis and cell division. To do this we must examine the chromatin of the nucleus. Chromatin consists largely of deoxyribonucleoprotein, but on the basis of his histochemical test as applied to isolated nuclei, Brachet has concluded that chromatin also contains a small amount of ribonucleic acid, and has confirmed this by direct pentose estimations on isolated nuclei. He claims that 10 per cent. of the total nucleic acid content of nuclei is ribonucleic acid (Brachet, 1941 *a* and *b*).

A more detailed histochemical examination of the chromatin in the cells of the salivary gland of the grasshopper, which are particularly convenient to work with, has led him to suggest that the ribonucleic acid of the nucleus is found along with deoxyribonucleic acid in the *heterochromatin*, while the *euchromatin* contains deoxyribonucleic acid alone. This fits in very well with the views of Caspersson (1941) who has used entirely different methods. He maintains that the *euchromatin* consists of discs rich in deoxyribonucleic acid alternating with achromatic regions made up of higher proteins of the globulin type. On the other hand the *heterochromatin* consists of histone, deoxyribonucleic acid and probably a small amount of ribonucleic acid. The nucleolus contains histone, ribonucleic acid and higher proteins of the globulin type. Where chromosomin fits into this scheme is not yet clear. It may be that chromosomin is related to the higher proteins of the globulin type, or it may be that the whole scheme will have to be revised in the light of Stedman's discovery.

Caspersson (1941), however, goes a stage further than this and has suggested that the most important centre for protein synthesis is the nucleus, particularly the chromatin. While the euchromatin controls the synthesis of higher proteins, the heterochromatin controls the synthesis of histones. These histones accumulate in the nucleolus

from which they diffuse out towards the cytoplasm. When they reach the nuclear membrane they induce the formation of ribonucleoproteins of the cytoplasm and these in turn stimulate the synthesis of cytoplasmic protein (Caspersson and Santesson, 1942).

This theory has still to be submitted to the test of rigorous experimental investigation, but, even so, it will serve as a pointer indicating the direction along which developments are likely to take place in the near future.

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SOME UNUSUAL FORMS OF DERMATITIS *

By ROBERT AITKEN, M.D., F.R.C.P.Ed.

I HAVE chosen some unusual forms of dermatitis as the subject of this lecture partly because of the puzzling nature of some of the eruptions and partly because of the lack of response of others to treatment.

I prefer the word "dermatitis" to "eczema." Those who use the latter term are not in agreement as to what it means. Some hold that eczema is due to internal causes alone and reserve the term "dermatitis" for those cases in which the cause is external. Others use the term "eczema" to cover those cases due either to internal or external causes. Those who use the word "dermatitis" in preference to "eczema" believe that it can be produced by either internal or external agencies.

DERMATITIS AUTOPHYTICA

The first type of dermatitis about which I wish to speak is that where the eruption is self-inflicted, dermatitis autophytica. This condition is a puzzling one to all who are not in the habit of seeing these cases. It is unusual for this condition to be diagnosed by the family doctor, and if he does suspect the true nature of the eruption he naturally hesitates to tell the patient's family. This is essentially a case where the responsibility should be shared with a consultant if the family doctor has come to the conclusion that the eruption is self-inflicted. The relations between the consultant and the patient and her family are more impersonal, and consequently the opprobrium of having made this diagnosis falls on him and not on the family doctor whose task in these cases is a most difficult one. In most cases, however, the doctor has no suspicion of the real nature of the condition and sometimes even refuses to believe the consultant.

The picture which is presented in dermatitis autophytica is of the most varied nature. Sometimes when taking the history from the patient it is observed that she is rather furtive and will not look at the doctor. In other cases the patient is most anxious to show the eruption, especially if there is an audience, such as a class of students. This exhibitionism should always tend to put one on guard.

I have here some lantern slides in natural colour which will show better than any verbal description the curious and varied nature of the eruption. The first picture shows the forearm with a series of short red lines running *across* the limb. The lines suggest the use of a sharp instrument, such as a razor blade, as the causal agent.

* A Honyman Gillespie Lecture delivered in the Royal Infirmary on 22nd February 1945.

The second slide shows an entirely different picture. Here there is a circular patch on the forearm with a redder edge. At first sight this might seem to be a patch of ordinary dermatitis or even of ringworm of the body, but there is something in the appearance which does not fit in with the diagnosis of either of these conditions. Here it would seem that the forefinger of the other hand had been worked in a circle applying a caustic.

In the third case the eruption is again different. Here, too, the forearm is affected, but in this case it is the right arm and lesions are found on the upper arm also. The forearm has obviously been held across the body as in the picture and something held in the left hand has been moved horizontally to and fro across the body. This gives rise to the lesions up and down the forearm and across the upper arm. No ordinary skin eruption would follow that pattern.

The fourth slide again gives a different picture. Here the left side is affected but the lesions are of a deeper type as though a pointed instrument, such as a pair of scissors, had been forced into the skin.

The next slide shows both forearms affected, and the early and late lesions are clearly seen. On the left forearm there is a swollen red patch, and I would draw your attention to the square shape of the patch with its sharply demarcated edges. It is obvious that in this case a piece of material soaked in some irritant or caustic fluid has been applied to the forearm. A more prolonged application leads to the formation of a slough such as is seen in two of the lesions on the right forearm. In the third lesion on this forearm the surface left after the separation of the slough is shown. I would draw your attention to the square shape of these lesions also. This girl knew that we had recognised the nature of the lesions as, when she was told to wait so that she might be admitted to the ward, she slipped away and did not visit the department again.

The last slide of this series shows more extensive mutilation; this time of the abdomen and thighs. Some of the lesions are faint and are obviously in process of healing while others are more recent. The appearance suggests that the fingers had been dipped in some irritant fluid, then drawn across the body. On the upper abdomen the marks are horizontal, and as the thighs are approached they take a more vertical position.

It is not usual to have the face affected in these cases, though I have seen one case in which the forehead alone was involved. No area of the body is immune, however, and all sorts of implements may be used to produce the eruption. Here, for example, is a cast showing lesions made by heated curling tongs, and the direction of the linear marks easily gives the clue as to how they were produced.

In 1941 I was asked to see a girl at one of the E.M.S. hospitals. The doctor who asked my help was a member of the peace-time staff. The patient, according to his description, had a series of sharply punched out ulcers on the back of the left hand with bridges of healthy

skin between them. I had no hesitation in diagnosing from his description that it was a case of dermatitis autophytica, and examination of the patient confirmed this. My resident at the hospital tried to find out the motive behind the self-mutilation, and she eventually succeeded. The girl had been employed in the hospital but was about to be dismissed. She had fallen in love with one of the attendants at the hospital and did not wish to leave. The eruption was produced with small crystals of sodium carbonate strapped to the back of the hand, and as the lesions looked very sore she was kept in the hospital as a patient. She was not confined to bed, but was allowed out into the grounds where she was able to meet her beloved.

This is one of the few cases that I have met where the patient admitted producing the eruption. Most of them deny it. Numerous cases have been subjected to psycho-analysis but no help has been obtained from this procedure.

In my experience the ordinary case of dermatitis autophytica shows an anæsthetic palate and conjunctiva, and these are useful in corroborating the diagnosis in a doubtful case. All these cases met in the ordinary way are hysterical and the eruption is merely one phase of this condition. They require a thorough overhaul and should not merely be abruptly dismissed as frauds. Sometimes the motive is easily found, but in most cases it is obscure. Some years ago I abstracted from a French dermatological journal notes of a case of intractable ulceration of the fingers where two fingers had been amputated. Ulcers had now appeared on a third finger, and the surgeon intended to remove this one also, but before doing so he asked a dermatologist to see the girl. The dermatologist had no hesitation in diagnosing dermatitis autophytica, and it was proved later that the ulcers were due to the use of caustic potash. The mental imbalance in this case was carried some degrees beyond hysteria. For two or three years this patient had been living in nursing homes at the expense of her people and, when their resources were at an end, in hospitals at the public expense.

Another case that I recall demonstrates two points, first the motive and secondly how a little more thought on the part of a doctor would have led to a modification of the diagnosis given. Some years ago I was asked by an Insurance Company to examine a girl on their behalf. The history that the girl gave was that about the middle of December, eighteen months before, a hot-water bottle burst and burnt her while she was in bed. She continued at her work as a domestic servant for a week, and then the feet became so raw and painful that she had to give it up. Four months later she was still off work, and she was then examined on behalf of the Insurance Company by a physician who certified that the condition of her feet and legs was caused by the scald. Within a month of this examination the areas were healed up and she resumed work. Towards the middle of the following December the scars broke down again, and once more she had to give up work.

It was the following March or April that I examined her. She had then a series of small circular scars in a straight line up the middle of the right calf with a smaller scar in the centre of the dorsum of the right foot. In the region of the left internal malleolus there were three scars set in the shape of a triangle with one on the dorsum. There could be no doubt of the diagnosis. The eruption was a self-inflicted one and was produced, I should think, by a stopper or cork dipped in a caustic such as lysol. A moment's thought will show conclusively that no matter how the girl was lying in bed when the hot-water bottle burst—if it ever did burst—the resulting scald could not possibly give rise to a line of equal-sized circular scars. The motive in this case is clear: the girl wished to have Christmas and New Year at home—and with compensation as well. It is of course possible that there was a scald originally, and this suggested to the girl the idea of irritating the leg so as to get home for the festive season. The so-called breaking down of the scar was simply another application of the caustic, again shortly before Christmas. Incidentally, this girl took about £70 altogether from the Insurance Company.

So far all the patients I have referred to have been women, and in normal times it is only in women and girls that this type of eruption is seen. These times are not normal, however, and I have seen two cases in men within the last few years. They were both soldiers whom I had under my care at an E.M.S. hospital. In the first case the patient, who had been transferred from a hospital in the West to make way for air-raid casualties, stated that five years earlier he had had his appendix removed and that all had been well till a few months earlier when the scar had broken down. On examination there were seen several punched-out ulcers round the appendix scar. The appearance suggested a tertiary syphilide, but treatment with mercury and potassium iodide did not bring about any improvement. I was puzzled at the persistence of the condition, and then one morning I observed a small shred of sloughed skin. Questioning of my Ward Sister afterwards elicited the information that the slough had appeared between the morning and the evening dressings. The diagnosis was at once obvious as no skin disease will produce a slough on healthy skin within twelve hours unless the patient is gravely ill.

In the other case the man had large bullæ on one leg. Here there was no doubt about the diagnosis, and it was eventually proved. When taxed with the matter, the man admitted that he had been responsible for the eruption. In both these cases the incident was not reported to the authorities. If this had been done the man would have been placed in some prison camp and his object, the dodging of military service, would have been partially achieved. I told the man that he would get a chance to make good, but that he must not think that he could go on deceiving his medical officers as he had succeeded in doing in the past. A note written in large letters in red ink was to be inserted in his medical history sheet to the effect that if any

eruption appeared again, his medical officer was requested to communicate at once with the superintendent of the hospital where I had seen him.

Light Dermatitis

The second type of dermatitis to which I wish to refer is that produced by light. Ordinarily we look on light as something beneficent and are apt to forget that it can be an irritant to some people. In this form of dermatitis the eruption appears on the exposed parts, the hands and face. The eruption begins as a rule in childhood and is known as Hutchinson's summer prurigo, after Jonathan Hutchinson, who described it. The condition becomes apparent in March or April when the actinic rays of the sun begin to gain strength and it lasts till September or October, the duration depending on the type of weather prevailing at that time of the year. Remaining away during the late autumn and winter it recurs each spring. The eruption consists of groups of papules and vesicles. There is a somewhat similar condition known as *hydroa vacciniforme*, but this I believe to be merely a more severe stage of the summer prurigo. It is preferable to drop these other terms and refer to both conditions as light dermatitis.

This condition is due to some toxin circulating in the blood and sensitising the skin to the actinic rays. As long ago as 1898, McCall Anderson, a Glasgow dermatologist, drew attention to the fact that in some of these cases there was present hæmatoporphyrinuria. This observation made so long ago is interesting in the light of modern knowledge. It is now known that eosin, hæmatoporphyrin and allied substances, if injected, sensitise the skin to light. This, however, does not explain all the cases of dermatitis due to light. In some cases it would seem as though ordinary bread were the sensitising agent. It is known that in America buck wheat cakes sensitise some people to light. A good many years ago, arguing on a similarity between the two grains, I advised that a boy who suffered from light dermatitis be given no bread or any foodstuff which contained ordinary flour. He was to eat rye bread and oatcakes and no other form of breadstuff. All through the late spring and early summer of that year the boy improved, but he relapsed soon after going on holiday. He had gone to a small village where it was not possible to obtain ryebread or oatcakes and consequently he had to eat ordinary bread. A recurrence of his light dermatitis was the result.

In other cases the sensitising agent would appear to be a toxin absorbed from fæcal material that is neutral or alkaline instead of the normal acid. I will quote one case. A girl had a light dermatitis and her doctor was asked to test the reaction of her stools. A few weeks later he reported that the stools were still alkaline, but that since the treatment I had advised had been instituted there had been a considerable improvement in the girl's condition in spite of the fact that the weather had been bright and sunny and, in the doctor's words,

the type of weather which always made her worse. I took the girl into my ward, and under treatment the stools became acid. She was then told to sit out on the balcony, which faces south, on the first bright sunny day. This she did and the skin merely reddened instead of the papules and vesicles appearing. I then stopped the regime so as to allow the stools to revert to the alkaline state, when I would make a further exposure of the skin to the sun. Unfortunately from the scientific point of view, the girl's home conditions required her return before the stools became alkaline again and so definite proof could not be obtained. It is a line of investigation, however, which is worth pursuing.

Folliculitis Decalvans

The next form of dermatitis about which I wish to speak is one which occurs on the scalp. It is an organismal infection of the hair follicles, and the clinical picture varies from a few follicular lesions to the involvement of practically the whole scalp. In the mildest states there is merely slight redness round the follicles with the hair in the centre of the red area. A more advanced stage is where the redness is more intense and a pustule forms in exactly the same way as is seen in sycosis. Still only a few follicles may be involved. In the most advanced stage the pustules are numerous, there is destruction of the hair follicles and a scar results. This is the picture which is seen in what was formerly known as folliculitis decalvans, but it is essentially the same condition as the milder forms which I have already mentioned. The condition is not a common one even in its mildest form and fortunately the most advanced stage is, in my experience, rather rare. So far all the cases that I have encountered have been in men.

Treatment even in the mildest forms of the disease is difficult. The real difficulty is the presence of the hair, but even when the hair has been removed by epilation the cure is not easy. Few patients care to have the hair cut really short and kept short, while it is unusual to meet a patient who is prepared to have the scalp shaved and kept shaved regularly over a period of some months. Unless one of these methods is adopted no form of treatment has much chance of success. Some years ago I had several patients with this condition, fortunately in a comparatively mild form and over only the front of the scalp. The only treatment that I found of any real value was ultraviolet irradiation of the part of the scalp affected.

Last year I had under my care in one of the E.M.S. hospitals a soldier who had the whole scalp affected, though the condition had not gone on to scarring. The usual remedies made little impression and neither did vaccines nor ultraviolet radiations. A medical officer, who was regularly visiting my clinic at the hospital, asked if sulphothiazal would not help. In similar conditions on other parts of the body my experience with this remedy had not been favourable, but

I was prepared to try anything which might help the young man. I suggested that the medical officer should treat one side with his remedy, and that I should treat the other as a control. After a month's trial the doctor had to admit that the side that he was treating was not so well as my side. The causal staphylococcus was found to be penicillin sensitive and this remedy was then applied to one side by the penicillin expert at the hospital, the other side again being used as a control. After two months there was no improvement; indeed, the side treated with the penicillin was worse than the other. The hair over the whole scalp was then epilated with X-rays and this brought about an improvement, the penicillin and other treatment being continued. The improvement was only temporary and as the hair grew in the condition became worse, the deterioration being more marked on the penicillin side than on the control. The organism was then found to have become insensitive to penicillin and that treatment was accordingly abandoned. Had the penicillin been given by the drip method, as I had suggested before this treatment was begun, it is possible that a greater improvement would have taken place. As it was, the man was little or no better than when he was admitted to hospital. Unfortunately, he had been boarded out of the army, and as the time after his discharge during which he could be kept in hospital had elapsed I had reluctantly to allow him to be discharged from the hospital, and so a further trial of penicillin after the organism had again become sensitive could not be carried out.

Pyoderma Gangrenosum

The next form of dermatitis I wish to mention is distinctly unusual. I have seen only three examples of this type. In 1934 a patient came to the Royal Infirmary with a group of lesions on the left leg. These consisted of a slough surrounded by a narrow ring of redness. There was no history of injury and the condition was painless. Under treatment the slough separated and the lesion presently healed. A year or two later I saw another patient, a woman this time, who presented a similar condition on the legs. Again there was no history of injury. In 1937 at the annual meeting of the British Association of Dermatology held in Edinburgh, Gibson of Manchester read a paper in which he described a similar case. His patient was a woman who gave a history of a swelling in the left groin which appeared suddenly and became ulcerated in a few days. Within two or three months other similar lesions appeared on various parts of the body. The lesions were distributed over the trunk and limbs, the face being free. All the lesions showed the narrow erythematous halo round the edge.

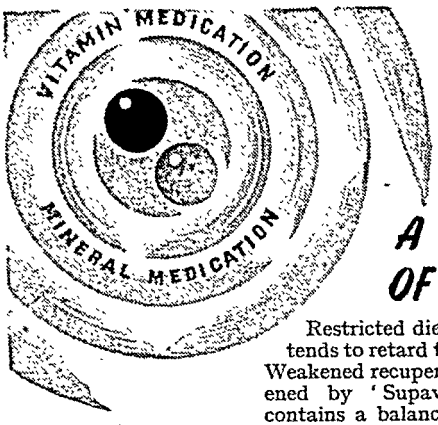
Gibson stated that the name Pyoderma Gangrenosum was given by Brunsting, Goeckerman and O'Leary to a series of 5 cases which they reported in the Archives of Dermatology and Syphilology in

October 1930. The name is merely a clinically descriptive term. Four of these cases were associated with an ulcerative colitis and the fifth with empyema. In the colitis cases the lesions began as pustules which presently assumed the appearance of a slough surrounded by a narrow halo of redness. In each of these cases there was a close relationship between the medical condition and the skin lesions. An aggravation of the colitis was associated with a worsening of the ulcerated areas, and as the patient's general condition improved the skin condition improved also. In the empyema case the lesion began at the edge of the drainage sinus and gradually extended till the greater part of the abdominal and lower thoracic skin was involved. In this case also there was a surrounding margin of redness, though not so intense as in the other cases. This last patient was under observation only a short time as he died after surgical intervention. The authors concluded that the skin lesions were part of a generalised infection characterised by marked lowering of the body resistance to the invading organisms and that successful treatment depended on complete control of the systematic disease.

Gibson also mentioned a case described by Lane and Stroud in 1933 in the same journal. This case was associated with a gall-bladder infection. In this case, too, there was extensive ulceration and multiple lesions. There was also the same close relationship between the general condition and the skin lesions. The primary lesion here was a papule which necrosed, the narrow ring of redness being present also.

In the discussion which followed Gibson's paper several speakers suggested that an injury preceded the skin lesions. With this view Gibson did not agree, and I was able to support his opinion, as a few months earlier I had seen in one of the medical wards of the Royal Infirmary an elderly man who showed a most interesting picture. I cannot at this date recall the condition for which he had been admitted to the hospital, but while in the ward he had developed purpuric spots of various sizes on the lower abdomen, thighs and legs. Some of these showed the definite necrotic change I have indicated, and each of these areas showed the narrow ring of redness which is seen so clearly on the lantern slide which I have shown.

Gibson's case and those of the American observers resemble the two recorded in 1903 by Allan Jamieson in the *British Journal of Dermatology* under the title of Ecthyma Terebrans. Jamieson's first case was a woman worn out with overwork. The condition began as a red spot on the left breast. The lesion soon became pustular. Another lesion appeared on the back between the scapulæ and another on the left leg. All these spots became pustular and soon broke down to form ulcers. There was no inflammatory halo in this case round any of the lesions. Jamieson's second case was a child of 21 months. The condition began like impetigo, but presently pustular lesions appeared, ulcers formed with a black crust in the centre and a narrow red halo. In this case the lesions were on the face, thighs and legs.



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Jamieson stated that the earliest description of this form of ecthyma was given by Professor Isidor Neumann in his *Atlas of Skin Diseases* published in 1885-89. In Neumann's cases there was necrosis of the vesico-pustule and a red halo round the lesion. Neumann mentions that there is a variety peculiar to children. In this type the lesions are primarily pustular surrounded by a red areola. Sabouraud, according to Jamieson, has given the most complete description of this condition in his book *La Pratique Dermatologique*.

There is thus a great similarity in the appearance of the American cases and those described by Neumann in his Atlas. Jamieson does not mention necrosis in his first case, but merely states that the pustule soon formed an ulcer. In this case, too, there was no red halo. His second case conformed more to Neumann's description. Gibson's case also resembled Neumann's.

The two earlier cases that I had seen differed from the American cases and from Gibson's in that there was no systemic condition associated with the skin disease. The fully developed lesions certainly conformed to the appearance of Gibson's case and also to the American ones. They also conformed to that described by Neumann. All the lesions were fully formed when I saw these two cases, so that I cannot say from what primary lesion they developed. It may be that my two earlier cases are of a different origin from the others that I have mentioned, but I think that this is unlikely. The central slough surrounded by the narrow halo of inflammation was identical in all the three cases that I have seen. The condition is obviously an unusual one and a considerable time may elapse before the various cases can be satisfactorily correlated and the true nature of the condition determined.

THE PROBLEM OF ORAL INFECTION AND ITS RELATION TO SYSTEMIC DISEASES

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RECENT advances in oral pathology tend to emphasise again and again the hitherto neglected factor of oral infection as being of importance in the differential diagnosis of a score of systemic diseases.

I shall try to give here a short résumé of this vast subject based partly on my own investigations.

Etiology of Oral Infection.—Much work has been done in order to explain the etiology of oral infection and to determine the nature of the focus of infection.

A definition offered by Billing describes a dental focus of infection as a strictly limited amount of parodontal tissue infected by certain pathogenic bacteria. There are primary and secondary foci. The former may be found not only in the oral cavity and teeth, but also in other organs of the body. The latter is either a direct continuation of a primary focus or is the outcome of lymph- or blood-stream dissemination. The damage done to the body by real bacterial metastases has to be discerned from the toxic effects of the primary focus on the distant organs of the body.

Bacterial metastases, from the above-mentioned foci, tend to form emboli in the distant parts of the body, particularly in small vessels.

Clinical experience shows that after a source of infection, such as a diseased tooth, has been removed, functional or at times even organic changes caused by toxins from that particular focus subside quickly provided there were no metastases present.

Some German authors have attempted to explain the nature of focal infection on the lines of allergic phenomena that take place in the body in response to bacterial allergens.

Former assumptions that bacterial metastases from the primary dental focus are formed only during the acute stage of inflammation have proved to be incorrect. It is common knowledge to-day that dissemination of bacteria from chronic dental foci may follow even as slight a disturbance as the pressure on the teeth during mastication. Such factors, of course, as unhygienic habits, malnutrition, etc., help to bring about a general infection, which is the final issue in non-resistant individuals.

Foci of Infection.—Practically any organ of the body can be the seat of a focus of infection, the most dangerous foci, however, being those connected with teeth. Their origin can usually be traced to deep caries, which ultimately causes the pulp of the affected tooth to die. Gases evolved by bacteria in the gangrenous pulp force the

infected masses through the apical foramen, thus causing well-known periodontitis. Meanwhile defensive powers of the body come into play. Periodontal membrane thickens considerably. Granulation tissue is formed around the apical foramen as a measure to limit the further advance of bacteria. The above process is essentially chronic and produces a picture clinically known as periapical granuloma.

In the majority of cases the process advances a step further, leading to strong inflammation, the involved tooth becoming exceedingly tender and the patient suffering from considerable pain, which disappears as soon as a fistula is formed, and from this moment the process becomes chronic again.

There prevails a common belief that pulpless teeth that do not show any radiological changes cannot act as foci of infection. The conception is wrong, since the formation of an apical granuloma deprives the body of its second line of defence against bacterial invasion.

The reason why in some cases a granuloma does not develop is rather obscure. Sometimes the cause may be traced to the general lack of resistance of the individual due to exhaustion and debility.

Infection may also reach deep-seated tissues by the parodontal route, when the cingular ligament binding the gum firmly to the neck of a tooth becomes loosened. Causes leading to the destruction or loosening of the cingular ligament are lack of hygienic habits with regard to the mouth, accumulation of tartar, the overhanging of fillings, etc., causing inflammation of the gum and consequent formation of pockets (parodontitis).

Other common foci of infection are alveolar pyorrhœa and septic tonsils. Cook, Stafne and many others have been able to isolate from the parodontal pockets of persons suffering from pyorrhœa such organisms as *Entamœba gingivalis*, *Bact. fusiformis*, *Spir. dentium* and *Streptococcus viridans*. My own investigations have confirmed the above findings, *Streptococcus viridans* being the most common. Hartzel and Henrici were able to isolate staphylococci and streptococci.

Tonsils play an important part as a source of focal infection. Bacteria contained in the deep lacunæ can easily reach the blood-stream.

The list of the infective foci will not be complete if foreign bodies, such as fractured roots, fragments of fillings, retained and impacted teeth, are not mentioned. All types of gingivitis and stomatitis of long standing should be regarded, too, as serious foci of infection.

From the extra-oral chronic foci of infection the colon, appendix, prostatic gland and vagina are the most common.

Bacteriology.—Micro-organisms responsible for oral infection may conveniently be divided into two groups.

1. Proteolytic or pus forming, and
2. Non-pus forming micro-organisms.

Proteolytic micro-organisms can be found in acute inflammations of the mucous membranes with a tendency to ulceration and exfoliation

of the epithelium. These lesions usually cause much distress to the patient, but heal easily under the appropriate treatment.

Inflammations caused by the bacteria classed in the second group are milder in character. Bacteria of this group thrive on food débris and have a tendency to descend to the deeper parodontal tissues. *Streptococcus pyogenes*, *Staphylococcus pyogenes* (*albus* and *aureus*), and *Bact. pyogenes* are representatives of the first group, while *Streptococcus viridans* is the most typical of the second group.

It is known that *Streptococcus viridans* is easily able to penetrate deep tissues and blood-vessels. Hence it is very often found in general infection.

The mild type of inflammation caused by streptococcal infection is particularly dangerous, as it can easily be overlooked. The danger is more obvious when it is realised that a mild inflammatory response of the tissues is more liable to occur in debilitated individuals whose natural defensive powers are at a low ebb.

Once micro-organisms invade the pulp of a carious or otherwise damaged tooth, they face the defensive system provided by the formation of granulation tissue around the apex of the tooth. The further progress of infection is thus checked, at least for the time being. However, if in spite of that, bacteria succeed in multiplying, further means of defence are provided. The infiltration of lymphocytes and leucocytes supervenes, and in time a thick fibrous capsule is formed around the apex, thus providing a more effective obstacle to the further progress of the bacteria. Often, however, a certain number of bacteria manage to cross this barrier and reach the blood-stream. Hence all granulomata should be regarded as potential foci of infection.

Pathogenic bacteria can easily be isolated from the periodontal membrane of pulpless teeth. The prevailing organism is *Streptococcus viridans*.

It is interesting to note that *Streptococcus viridans*, in spite of its low virulency, is found to be the cause of death in many cases of general infection. The latest work of Solowey shows that there is no difference whatsoever between a *Streptococcus viridans* found in the heart lesions of endocarditis and that in the throat or in the oral cavity.

Why *Streptococcus viridans* should be associated so often with endocarditis may be explained by the fact that it is one of the commonest organisms of the oral cavity. Congenital heart defects and damaged valves yield easily to bacterial endocarditis. Many cases of bacterial endocarditis have been observed, following the extraction of teeth in individuals with septic mouths. *Streptococcus viridans* was found invariably at the post-mortem. Not infrequently healthy valves are attacked by *Streptococcus viridans*.

I have carried out bacteriological studies on hundreds of extracted teeth from patients suspected of suffering from oral infection. All of the teeth before extraction were tested for vitality of the pulp. Every tooth was X-rayed. Special precautions were taken to avoid contamination during extraction. A careful case history was obtained

of each case. Most of the teeth possessed fillings, and many were root-canal fillings. As controls, normal teeth were extracted and examined whenever it was possible. Ninety-two per cent. of the pulpless teeth yielded pure colonies of *Streptococcus viridans*, 3 per cent. colonies of *Streptococcus hæmoliticus*, and the remaining cases mixed colonies of *Streptococcus viridans*, *Staphylococcus aureus*, *Streptococcus hæmoliticus*, *Bact. mesentericus*, etc. It is noteworthy that once *Streptococcus viridans* is found in one of the pulpless teeth of an individual, all his remaining pulpless teeth extracted at different appointments will show the same contamination.

The above findings have been confirmed by Russian workers.

Teeth with vital pulp are always sterile. If bacteria are found in such teeth a contamination is certain to have occurred during extraction or afterwards. Teeth with living but diseased pulp may be positive bacteriologically. The bacteria in this case are derived from diseased periodontal membrane.

Influence of the Dental Focus of Infection on other Organs of the Body.—Greatly divergent views are held as to what systemic diseases may be attributed to a dental focus of infection, some authors believing that only certain affections may be thus produced, and others maintaining that almost any kind of disease may be traced to this cause.

Many of the lately published works recording results obtained after the eradication of primary foci of infection seem to corroborate the view that much more attention should be paid to the teeth and the oral cavity as an etiological factor in many systemic diseases.

The following have been observed to be caused directly or indirectly by focal infection from the teeth and the oral cavity:

Alimentary System.—Dyspepsia, flatulence and anorexia may often be attributed to the swallowing of pus from pyorrhœa alveolaris. Duodenal or gastric ulcers, as shown by Rosenow, may be experimentally produced by injecting intravenously virulent bacteria obtained from a dental focus. Out of 66 animals injected by Nakamura with streptococci collected from the tonsils of patients suffering from gastric ulcer, 70 per cent. developed a gastric ulcer.

It is thought that some cases of chronic ulcerative colitis might have their origin in focal infection. In a series of experiments, Bergen proved that colitis can be caused by non-hæmolitic streptococcus, of the same type found in dental foci. Bergen concluded that after dental foci had been eradicated and the patient injected with a proper amount of autogenous vaccine colitis would promptly subside.

Less frequently appendicitis and cholecystitis may be directly due to metastases from a dental focus of infection, such cases, however, being very rare. A case of hepatitis traced to alveolar pyorrhœa has been recorded by Barker.

Steadman has suggested that dental foci of infection, and alveolar pyorrhœa in particular, may play a part in the formation of cancers in the alimentary canal. According to him a large percentage of people suffering from pyorrhœa are cancerous, because continual swallowing

of septic masses causes gastritis, and in many cases this may precede the actual development of cancer.

Kidneys.—Glomerulonephritis often has its origin in oral infection. The acute glomerulonephritis following scarlet fever is a typical example, where the primary focus is in the tonsils. Possibly dental foci may be responsible to some extent for nephrosis and chronic diffuse nephritis. It is now known that pyelitis and pyelonephritis are often caused by streptococcal or staphylococcal infection and not so much by *B. coli* as was formerly thought. Meisser and Bumpus were able to produce pyelitis by transferring bacteria from dental foci to the ureters. The above was confirmed by Haden.

Anæmia.—Secondary anæmia is often the chief finding in oral infection. According to Haden, thrombocytopenic purpura may be similarly caused.

The Heart and Blood Vessels.—Bacterial endocarditis is always associated with some distant primary foci. In young people the foci are usually situated either in the tonsils or in adenoids, but in adults dental infection is usually responsible. Bacterial endocarditis progresses rapidly and as a rule is fatal.

Myocarditis may sometimes develop simultaneously with rheumatoid arthritis. This complaint will follow a long period of absorption of toxins from chronic dental foci. Cardiac arrhythmias may be also traced sometimes to the same cause. Divergent views are held as to whether hypertension is occasionally caused by dental infection, but this is perhaps going too far.

Arthritis.—With the exception of acute rheumatic fever, all other types of joint affections may have some connection with dental foci of infection. Barker and Willcox are in favour of the above view, while Cecil, Archer and others maintain that only 30 per cent. of chronic joint affections are so connected.

Infective arthritis develops either in consequence of the lodgment of bacteria in the joints or surrounding tissues, or it may be due to absorption of toxins from distant foci.

Lately accumulated evidence seems to suggest that rheumatic fever and, less so, rheumatoid arthritis are caused by a filtrable virus. If this is so, we may assume that in this case infective foci are the activating agents.

Diseases of the Nervous System and Mental Disturbances

Polyneuritis and neuralgia of the trigeminal and sciatic nerve have been known to develop from oral infection. Symptoms of neurasthenia may develop due to the slow absorption of toxins from infective foci. Cotton and Graves observed good results in mental patients after their diseased teeth had been extracted.

Eyes.—It is a well-known fact that many eye diseases have their origin in focal infection. Out of 100 cases of iritis and iridocyclitis

examined by Butler, 17 developed indisputably from oral infection, whilst 41 were probably of the same origin.

The routes by which infection reaches the eye from the teeth are described by Rowland as follows :—

1. After the destruction of the bone surrounding a tooth, infection reaches the eye directly.
2. Through or beneath periosteum.
3. By blood vessels.
4. By the lymphatics.

Sepsis.—Lassitude and occasional rises of temperature in otherwise healthy individuals may often be due to the slow but continuous penetration of bacteria from dental foci of infection into the general circulation. The symptoms increase according as larger masses of bacteria succeeded in reaching the blood-stream, a state known as bacteriæmia. As a rule the natural body defences represented by the blood, bone-marrow, liver and spleen usually succeed in destroying the bacteria. If, however, bacteriæmias tend to occur repeatedly, or if the general body resistance is lowered by other causes, the defences are easily overcome and a general infection of the organism results. In such cases a blood-culture is usually positive and the prognosis is very unfavourable if *Streptococcus viridans* is found.

Oral Infection in Children.—In 1882 Kaczorowski directed the attention of the medical world to the fact that even slight inflammations of the oral mucous membranes of a child have an enormous influence on the well-being and behaviour of the child. The child becomes restless and irritable and loses his appetite. The above observations have been entirely confirmed by recent writings.

I published a few years ago some cases of rheumatism in children which were cured after the extraction of diseased teeth. I should like to impress upon the reader the necessity of a proper diagnosis and treatment in diseases of the oral mucous membranes and deciduous teeth. Carious milk teeth present a serious potential focus of infection to the body as a whole; hence early discovery and treatment of caries in children is imperative.

Clinical Examination of Teeth.—Swelling and tenderness of the mucous membrane at the level of the apex of a tooth indicate that an active infective focus is present. Such a tooth is usually tender to percussion. The lymphatic glands draining the region of the seat of an infective focus are usually swollen and tender, this being particularly obvious in children.

There has been much discussion about what constitutes an active and what an inactive focus. It seems to me that any focus containing pathogenic bacteria is an active one and capable of infecting other organs of the body, even if it does not present any visible signs of inflammation.

Treatment.—As a first step all infective foci must be eradicated, and then general measures should be adopted to remove the effects of infection in distant parts of the body. The first part of the treatment

concerns the dentist, the second the doctor. To insure good results a close collaboration must exist between these two. As the dentist is not concerned with the general condition of the patient, he should consult the doctor before any serious operation to obviate the invasion of bacteria into the blood-stream of his patient at an improper moment. Such consultation is very important, if we remember that all patients suffering from oral infection have as a rule a less degree of resistance than healthy individuals.

Treatment will consist of :—

1. General measures to combat general effects of infection. Here autogenous vaccines and sulphonamides are of some value.
2. Local measures aiming at the eradication of infection. They may be: (*a*) Conservative or (*b*) Radical (Apicectomy, Extraction).

It is impossible to go into further details of treatment, as those are of interest to the dentist only. I may add that conservative measures are not very reliable, as proved by bacteriological studies. Most writers strongly object to any pulpless teeth being treated at all and recommend extractions or resection of the root whenever it is possible. The mere extraction of a diseased tooth and removal of the infective foci does not necessarily signify that the body is cleared of infection, as secondary foci may have formed already. This fact should, however, never provide an excuse for leaving an infective focus undisturbed, as even the most advanced cases of oral infection were cured after the primary foci of infection had been thoroughly removed.

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WOUND INFECTION

THE "TISSUE SWAB"

By H. L. DE WAAL, M.D., D.P.H., D.T.M. & H., Major R.A.M.C.
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INTRODUCTION

THE sulphonamides, acriflavine and penicillin are powerful weapons in the hands of the medical profession in combating wound infection. The problem is, however, far from solved. Every surgeon will from time to time become aware that all is not well in his wards—that infection is spreading from patient to patient, or that despite stringent aseptic technique and rigorous treatment, wounds remain infected. There is a tendency for those engaged in the study of wound infection to seek that "panacea" which, when applied to all wounds, whether large or small, deep or shallow, clean or suppurative, will induce healing. This is good, but it should be counterbalanced by a study of the physiological and pathological processes that take place in wounds—they are more fundamental, and a better knowledge of these things must favour a more rapid discovery of that "panacea."

Bacteriologists, biochemists and pharmacologists, physiologists, pathologists and surgeons each have their own criteria for the study of wound infection. Let them pool their ideas and their knowledge, and results will surely be better. Too often the surgeon regards these people in special departments of medicine as his technicians and not his colleagues and advisers: the bacteriologist is there solely to tell him what the wound microflora consists of, the biochemist and pharmacologist to supply him with the substances to attack this microflora, the physiologist and pathologist to evaluate the results of his therapy by biopsy or necropsy. This is wrong. The surgeon is working for the welfare of the patient; the wound comes first. The combined efforts of the medical profession is what the patient desires. Surgeon and "back-room boys" are equally important, for the one is dependent on the other.

In the past two main methods have been adopted in research on wound infection: one at the bedside, the other in the laboratory. The former is clinical and is concerned with the appearance of the wounds, their rate of healing, the local effects of surgery and alterations of treatment as observed in the wards, and the visible toxic effects of therapeutic substances upon the patients. The latter concerns itself with the study of the organisms in the wounds, their damaging effect upon the patient's tissues and those of experimental animals, and the influence upon the bacteria of bacteriostats and other agents.

It concerns itself with the physiology and pathology of the affected areas, and with the general metabolism, normal and abnormal. It can thus be appreciated that for a better understanding of the problems *in toto*, laboratory workers and surgeons must pull together. A close liaison is necessary. This appeal has been made before, it cannot be repeated too often.

This paper is mainly concerned with one aspect of the subject—the collection of material from wounds for bacteriological investigation.

Technique of Collecting Material from Wounds, and other Bacteriological Considerations

1. In fresh wounds two swabs were taken. One was rubbed over as much of the wound surface as possible prior to excision and cleaning. The second swab was taken in a similar manner after saline lavation and surgical treatment.

2. Older wounds showing no clinical evidence of infection were swabbed in a similar manner before and after being cleaned with saline.

3. Three swabs were taken of those wounds showing clinical infection. A small quantity of superficial pus was collected on the first, usually from an area showing most suppuration. The second was rubbed gently over the whole wound surface in order to obtain, as far as possible, a representative sample of the total microflora. After careful cleansing with saline, using many small balls of cotton wool or portions of gauze, the third swab was taken from areas freed of pus. Attempts were made to disturb a few granulations, and slight bleeding was regarded as favourable.

4. All swabs were examined by aerobic and anaerobic culture, on solid and in fluid media. This was done as soon as possible after collection. Results were recorded after twenty-four and forty-eight hours. Particular note was taken of the proportions the organisms bore to one another in the swabs from the same wounds.

5. The coagulase test was carried out on all identifiable staphylococci.

Bacteriological Investigations—Record of Results

In all 658 wounds were examined bacteriologically. These have been subdivided according to their age and degree of infection :—

(*a*) Fresh wounds seen within eighteen hours of injury (201).
(*b*) Wounds over eighteen hours but clinically not infected (54).
(*c*) Wounds clinically infected (403).

Summary of Results

1. Wounds examined by ordinary bacteriological means, 0-5 hours after injury, showed little infection.

2. Infection was observed in wounds examined 5-8 hours after injury (20·0 per cent.). Proportionately the organisms were very similar to those in "tissue swabs" taken from clinically infected wounds.

3. By the end of eighteen hours, 88·8 per cent. of wounds were infected. Nonpathogenic parasites and saprophytes were present in most of the wounds.

TABLE I

Showing the Bacteriological Findings in 658 Wounds

Type of Wound.	Total Number	Number Infected.	Percentage Infected.	Type of Infection.											
				Superficial Swabs.								Deep Swabs.			
				Total Surface "Comprehensive" Swab.				Surface Pus only.				"Tissue Swabs."			
				Haem. streptococci.	*Staph. pyogenes.*	Gram Negatives.	Other organisms	*Haem. streptococci.*	*Staph. pyogenes.*	Gram Negatives.	Other organisms.	*Haem. streptococci.*	*Staph. pyogenes.*	Gram Negatives.	Other Organisms.
Fresh—	201	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Seen within 0- 5 hrs. .	42	5	11·9	0	1	0	4	...	...	...	...	0	0	0	1
,, ,, 5- 8 hrs. .	70	14	20·0	3	4	2	12	...	...	...	...	0	1	0	2
,, ,, 8-18 hrs. .	89	79	88·8	11	10	11	71	...	...	...	...	4	4	1	13
Old—	457	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Clinically not infected	54	42	77·8	3	6	1	42	...	...	...	...	3	3	0	11
Clinically infected .	403	403	100	108	81	51	394	51	78	50	394	90	72	24	94*

* In "tissue swabs" when *very few* "other organisms" were found in comparison with the numbers of hæmolytic streptococci, *Staph. pyogenes* and Gram negatives, they were ignored.

TABLE II

Showing the Percentages of the Various Types of Organisms from Different Parts of 403 Clinically Infected Wounds

Part of Wound Swabbed.	Percentages of Various Organisms Isolated.			
	Hæmolytic Streptococci.	*Staph. pyogenes.*	Gram Negatives.	Other Organisms.
Whole surface—"Representative swab"	26·8	20·1	12·7	97·8
Surface pus only . . .	12·7	19·4	12·4	97·8
Cleaned surface—"Tissue swab"	22·3	17·9	6·0	23·3

4. A marked decrease of organisms was observed in fresh wounds following cleansing and surgical excision.

5. The "comprehensive swab" showed that 77·8 per cent. of clinically uninfected wounds contained bacteria. Most of these were non-pathogenic. The majority of these wounds were under treatment when first seen.

6. All clinically infected wounds (403) yielded bacteria on culture. A notable difference in the relative proportions of the various types of organisms was observed in the surface pus, the "comprehensive swab" of the whole wound, and the "tissue swab." The most striking difference in the latter lay in the relative decrease in the number of non-pathogenic bacteria and the relative increase in the number of hæmolytic streptococci; *Staph. pyogenes* remained more or less constant.

7. The total number of colonies cultured on solid media from swabs taken after the saline cleansing of wounds ("tissue swabs") was greatly reduced in numbers in many cases, but the procedure yielded a higher percentage of the more pathogenic "tissue invaders."

8. Subculture from primary fluid cultures on to solid media gave a completely erroneous idea of the relative proportions of the various organisms.

Discussion

The usual method of taking wound swabs is open to much criticism, since it fails to give a true interpretation of what really is occurring in the tissues; which after all is the most important single factor in assessing what best can be done to promote healing.

The real interest of the clinical bacteriologist and the surgeon lies in the spreading or invading edge of an infected lesion, not so much in the pus that accumulates on its surface. In this pus there may be numerous organisms, and apart from those also present in the tissues some may have a decided nuisance value by producing proteolytic and saccharolytic enzymes, but the main problem is still the organisms that are penetrating, devitalising and killing the tissue cells. To take a swab of the pus only may "lead one up the garden path."

It is well to mention at the outset that the spreading edge of a wound is not only at the superficial periphery—the skin edge—but also downwards into the tissues.

From the experimental data to hand it appears necessary to take two swabs in studying the microflora of infected wounds: the first should be the "comprehensive swab," that is passed gently over as much of the wound surface as possible. This swab will give valuable data, for it tells one which organisms, pathogenic and non-pathogenic, are present in a wound. The second or "tissue swab" is that taken after the wound has been cleared of pus with cotton wool or gauze soaked in saline. It is rubbed more firmly over the non-pus parts; the granulations are "disturbed" and slight bleeding is indicative of the entry of the swab into the superficial tissues. Such slight bleeding may be regarded as favourable for it offers a better opportunity of reaching the organisms in the superficial cells. Vigorous swabbing over extensive areas is strongly deprecated, for such a procedure damages the reparative mechanism, and new portals of infection may be opened up—a procedure almost as bad as that of

removing adherent dressings without first soaking them loose. The object of the "tissue swab" is to get as close as possible to the organisms directly in the tissue without causing damage to the extent of delaying the healing process. *The careful removing of pus is thus the primary essential.* The greatest care should be exercised in swabbing those wounds liable to secondary hæmorrhage, and exposed blood vessels should be avoided. Furthermore, if a wound is healing no attempt should be made to disturb the delicate ingrowing epithelium.

The "tissue swab" yields far fewer organisms than the "comprehensive swab," but the proportions between the types of organisms in the two swabs are usually different. *This difference in proportions is the information that is of most value.* Thus, for example, the "comprehensive swab" may yield the following results: hæmolytic streptococci +, *Staph. pyogenes* ++, *Ps. æruginosa* ++, other organisms +++; and the "tissue swab": hæmolytic streptococci +, *Staph. pyogenes* +, *Ps. æruginosa* few, other organisms +. The "tissue swab" is relatively richer in hæmolytic streptococci, and the "comprehensive swab" in *Ps. æruginosa* and other organisms. Statistics drawn up on "comprehensive swabs" with results such as the above-mentioned would give undue prominence to *Ps. æruginosa.* The organism nearest and in the living tissue is the hæmolytic streptococcus. It is here the invading organism. Statistics compiled from similar "tissue swabs" would thus give due prominence to that organism. From this it may be argued that the "tissue swab" alone is of value. This is not so, for although it is the more important of the two, it frequently happens that an organism at one time proportionately high in the "comprehensive swab" may within a short period be prominent in the "tissue swab." The correct interpretation of the "comprehensive swab" may thus on occasions give the surgeon an indication of "evil things to come" and suggest the best line of treatment.

The following two cases illustrate these points fairly well:—

CASE I.—J. M., admitted to hospital with a lacerated, septic wound of the thigh which had been excised five days previously.

Comprehensive swab = HS ++. *Staph. albus* +++. Diphtheroids ++. Other organisms +++.
Tissue swab = HS +. *Staph. albus*, few. Diphtheroids, few. Other organisms +.

Of all the organisms present the hæmolytic streptococcus was flourishing most abundantly *in* the tissues. Sulphanilamide dressings were applied. Two days later swabs were again taken:—

Comprehensive swab = HS very few. *Staph. albus* +++. Diphtheroids +. Other organisms ++.
Tissue swab = HS +. *Staph. albus* +. Diphtheroids +. Other organisms +.

The hæmolytic streptococcus was still present in the tissues, but was disappearing from the pus. This may have been partly due to the action of the sulphanilamide. That the substance was not rapidly destroying the organism in the tissues was obvious.

Throughout this period the temperature swung between 100° and 102·8° F.

On the fifth day swabs were again taken, and showed a micro-flora very similar to that of the previous occasion.

Penicillin was applied locally, and swabs were obtained three days later. The hæmolytic streptococcus and staphylococci had disappeared from both swabs. The temperature by that time had dropped to normal. Healing was complete after three weeks.

CASE 2.—P. L., admitted to hospital with a grossly infected wound of the forearm. The temperature was 101° F.

Comprehensive swab = *Staph. pyogenes* +++. Other staphs +++.
Ps. æruginosa ++. Other organisms ++.
Tissue swab = *Staph. pyogenes* +. Other staphs, few.
Ps. æruginosa +. Other organisms, few.

There was relative increase in the numbers of *Staph. pyogenes* and *Ps. æruginosa* in the tissues as compared with the pus.

Penicillin was applied and two days later the results were :—

Temperature, normal.
Comprehensive swab = *Staph. pyogenes*, very few. *Ps. æruginosa* +++. Other organisms +++.
Tissue swab = *Staph. pyogenes* +. *Ps. æruginosa* +. Other organisms +.

A relative increase of *Staph. pyogenes* was present in the tissues, but had largely died in the pus.

After a further two days the results were :—

Temperature, normal.
Comprehensive swab = *Staph. pyogenes*, nil. *Ps. æruginosa* +++. Other organisms +++.
Tissue swab = *Staph. pyogenes*, nil. *Ps. æruginosa* +. Other organisms +.

The relative proportions of bacteria in the two swabs were identical, but as compared with the previous swabs *Staph. pyogenes* was no longer present in the tissues.

Penicillin treatment was stopped and a hypertonic mag. sulph. dressing applied "to clean the wound."

Thirty-six hours later the following findings were obtained :—

Temperature, normal.
Comprehensive swab = HS +. *Staph. albus* +. *Ps. æruginosa* ++. Other organisms +++.
Tissue swab = HS, nil. *Staph. albus*, very few. *Ps. æruginosa* +. Other organisms +.

Mag. sulph. dressings were continued, and on the following day the temperature rose sharply to 103° and the wound looked inflamed.

Comprehensive swab = HS ++. *Ps. æruginosa* ++. Other organisms +++.
Tissue swab = HS +. *Ps. æruginosa* +. Other organisms +.

The hæmolytic streptococcus, only present in the "comprehensive swab" the day before, was now in the tissues and was the obvious cause of the pyrexia.

Penicillin was again used, with rapid disappearance of the hæmolytic streptococcus and a return of temperature to normal.

Ps. æruginosa remained and the wound continued to suppurate.

After four days of penicillin therapy acriflavine (1/1000) was applied as wet dressings, and after a further four days the bacteriology was:—

Comprehensive swab = *Ps. æruginosa*, nil. Other organisms +.
Tissue swab = *Ps. æruginosa*, nil. Other organisms, few.

A sulphanilamide dressing was applied and the wound was not disturbed again for three weeks. The dressings were then carefully soaked off and healing was found to be almost complete.

Theoretical Considerations

A bacterial population growing in a favourable medium will increase to M-concentration. The organisms will occupy the whole of the biological space in the absence of any inhibiting factor. Thus in the superficial pus of a wound, consisting largely of dead leucocytes and tissue fluids, organisms of diverse types will increase rapidly. Saprophytes and harmless parasites, unable to survive in the living tissues, will flourish in such a medium.

Not all organisms have the same M-concentration, and it is known that those with the higher M-concentration will outgrow those of lower M-concentration. It is therefore not surprising that in the superficial pus large numbers of the more rapidly multiplying and hardier bacteria are to be found, and that they have frequently occupied the whole biological space at the expense of the more delicate pathogens. Micrococci, staphylococci, diphtheroids, gram negative bacilli and sporing aerobes are thus common in pus. "Delicate plants are choked by weeds in a garden, delicate pathogens are choked by saprophytes in a wound."

In the spreading edge of a lesion, at the point of invasion, things are very different. Here the pathogens, if they are invasive, have a biological space to themselves. Here their battle is with the body defences not with other bacteria. They prepare the soil for the less pathogenic species. So the lesion spreads; invasive organisms such as *Strep. pyogenes* lead, followed by less pathogenic types such as *Staph. pyogenes*, while above these in a dead medium of pus live the harmless organisms.

To arrive at a true interpretation of what happens in a septic

wound the pus must be cleared away and the tissue examined; "to see the delicate plants the weeds must be uprooted."

It is a most disturbing thought that perhaps the cumulative knowledge of years of intensive study of wound infection may be largely deprived of its value because of faulty technique in the taking of wound swabs. Most bacteriologists favour the pusy swab from a purulent wound. This investigation appears to show that swabs containing little or no pus, taken from cleaned suppurative wounds are of greater value.

Conclusions

1. The common method of examining only pus from wounds cannot be regarded as satisfactory.

2. The tissue below the pus is the important area to be swabbed for the invading organisms are here.

3. By taking two swabs: one of the entire surface before cleaning —the "comprehensive swab"—and the other of the tissue surface after saline lavation—the "tissue swab"—a comparison of microflora can be made, and details can be furnished as to which are the invading organisms and which the saprophytes. Also a truer estimate of the value of therapeutic agents can be arrived at. Further, the future bacteriological history of a wound can often be determined by a comparison of the findings in the two swabs.

Summary

1. Six hundred and fifty-eight wounds were examined bacteriologically and classified according to age and degree of infection.

2. "Comprehensive" and "tissue swabs" were taken in all cases.

3. The microflora obtained from each of these two swabs was compared in every case.

4. The errors arising out of taking a single swab only from the surface pus have been considered and the theoretical aspects of the matter have been discussed.

Acknowledgments

This article was written in the Field. My sincere gratitude goes to Sergeant V. Jones, Corporal S. Mitchell, Privates L. Winocour, and J. W. Cleak, and the other members of this laboratory who sacrificed much of their meagre spare time so that this paper could be written. I also wish to thank Private W. Harris for his assistance in preparing the manuscript.

NEW BOOKS

Cataract and Anomalies of the Lens. By JOHN G. BELLOWS, M.D., PH.D. Pp. 624, with 208 text illustrations and 4 colour plates. London: Henry Kimpton. 1944. Price 60s. net.

The scope of this book may be estimated by the following sentence from the foreword: "Certainly this material cannot be found elsewhere in a single volume or in many volumes." The first six chapters deal with the history, development, structure, composition, metabolism and developmental defects of the lens. In the next three chapters cataract due to pathological causes is discussed, and the last chapter of nearly 100 pages is devoted to senile cataract, including its treatment. The presentation throughout is excellent and each subject is exhaustively dealt with in detail. The illustrations are numerous, good and helpful. A valuable feature is the extremely full list of references to the literature, and there are excellent indices of authors and subjects. This book will be specially valuable as a work of reference and should be in the library of every ophthalmic surgeon.

Fractures and Orthopædic Surgery for Nurses and Masseuses. By ARTHUR NAYLOR, CH.M., F.R.C.S. Pp. xxii+288, with 243 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 16s. net.

The success of orthopædic surgery depends so much on the work of nurses and physiotherapists that the publication of such an authoritative book as this is a noteworthy event. This is especially so when one considers that in the general training of these workers the bare minimum of instruction is given. The book deals generally with the application of the principles of surgery to the orthopædic branch, and in particular to the three essentials of treatment—prevention of deformity, correction of deformity, and the maintenance of correction.

Orthopædic apparatus, technique, and methods of correction of deformity are dealt with in three excellent chapters, and thereafter the various orthopædic conditions are described in quite considerable detail and with many good illustrations which make the descriptive matter easily understandable. The author wisely pays special attention to those parts of treatment that are usually done by the technical assistants, such as the application of splints.

The book, as one would expect from the publishers, is beautifully produced, and in the opinion of the reviewer could be used with profit by medical students preparing for their qualifying examination. For nurses and physiotherapists there can be nothing better.

Surgical Disorders of the Chest. By J. K. DONALDSON, B.S., M.D., F.A.C.S. Pp. 364, with 127 illustrations. London: Henry Kimpton. 1945. Price 33s. net.

There is little doubt about the need for a book like this, since advances in the thoracic field have been so rapid in the last few years that the majority of surgeons have the greatest difficulty in keeping abreast of the voluminous amount of current literature on the subject. It is the responsibility of the specialist in chest work to assist the profession as a whole in learning to do well that work which is within their legitimate domain, and Major Donaldson, realising this, sets out to assist in this work and succeeds in doing so.

The book is written in three parts. The first deals with chest injuries and various surgical conditions of the chest wall, the second with non-tuberculous inflammatory conditions, intra-thoracic tumours, and congenital errors, while the third is devoted to collapse therapy in tuberculosis, with some comments on post-operative complications and anæsthesia.

An admirable broad outlook is taken on the treatment of the ordinary non-tuberculous empyema. The author says that the type of treatment may vary with

the type of nursing attention afterwards, since with unskilled dressings mixed infections are easily introduced.

The principle of the operative technique of lobectomy and pneumonectomy is discussed, and good line drawings to depict the anatomy necessary in a hilar ligation help considerably.

In the description of thoracoplasty for apical cavities a well-balanced review is given of the modern methods, and the author points out the dangers of the Semb type of operation, particularly in the presence of much peripleuritis. There is no doubt, however, that where it can be done it increases the probability of complete cavity obliteration.

This book amply fulfils the hope of the author to produce a somewhat epitomised volume dealing with fundamental advances in thoracic surgery. It is written so well that it is easily readable, and the production calls for no criticism.

The Premature Baby. By V. MARY CROSSE, M.D. (LOND.), D.P.H., M.M.S.A., D.R.C.O.G. Pp. viii+156, with 14 illustrations. London: J. & A. Churchill Ltd. 1945. Price 10s. 6d.

This book describes the methods of care and feeding of premature babies developed at the Sorrento Maternity Home in Birmingham. This Premature Unit, opened in 1931, has been under the medical charge of Dr Mary Crosse, author of the book, from the first up to the present time; and by 1943 the Unit had dealt with 2575 premature infants. The excellent results obtained are all the more impressive when it is realised that 85 per cent. of these infants were admitted to the Unit from their own homes.

The book is based on long practical experience of the problem of prematurity, and gives concise details of the whole technique of management and feeding of the premature from birth until the clinical condition warrants the return of the baby to its own home. The technique of management is described both as applicable to an institution and to the home. The author's methods are not complicated and can be carried out anywhere. The good results achieved are due both to the scientific soundness of these methods and no less to the thoroughness with which they have been carried out. The book deserves to be widely read and studied by all doctors and nurses who are responsible for the care of premature infants.

The Amino Acid Composition of Proteins and Foods. By R. J. BLOCK and D. BOLLING. Pp. xiv+396. Springfield, Illinois: Charles C. Thomas. 1945. Price $6.50.

Dr Block and Miss Bolling have produced a monograph which will be of very great value to all who are practically interested in the study of proteins and their composition. They give clearly written descriptions of the methods available for estimating the various amino-acids, and increase the reader's indebtedness by pointing out the difficulties and sources of error, and by indicating those methods which are the most reliable.

For each amino-acid they give tables of the percentages found in various proteins by different workers, and in each case they state the method used, indicate which, in their personal opinion, are the "best values," and give the mean with standard error. In a later chapter these mean values are collected in tables which summarise the available knowledge of the composition of many important proteins.

The authors rightly emphasise the importance of a knowledge of protein composition in nutrition, pointing out that, though other factors are concerned, the nutritive value of a protein depends on the "essential" amino-acids it contains. Accordingly they include calculations of the essential amino-acid requirements of man and of the quantities of these amino-acids supplied by various proteins.

Add to all this a comprehensive bibliography and a good index, and it is obvious that here is a veritable mine of information.

NEW EDITIONS

Synopsis of Obstetrics. By JENNINGS C. LITZENBERG. Second Edition. Pp. 405, with 157 illustrations. London: Henry Kimpton. 1943. Price 25s. net.

The author has by careful phraseology and the skilful use of tabulation successfully compressed a large amount of reliable information into a small, yet readable, volume. Its usefulness is enhanced by well-reproduced illustrations gleaned from text-books and journals. In presenting modern teaching and opinion, the reader's interest is increased by the introduction of the dates and sources of important contributions to obstetrical knowledge.

Although basically the essentials are similar to British teaching, the definitions and use of terms varies and might thereby confuse an unwary undergraduate preparing for a qualifying examination in this country. On the other hand, an experienced practitioner will find here a useful means of quickly refreshing his knowledge of the present-day opinion on obstetrical subjects.

Sick Children. Diagnosis and Treatment. By DONALD PATERSON, B.A. MANITOBA, M.D. EDIN., F.R.C.P. LOND. Fifth Edition Revised. Pp. viii+440, with 23 half-tone plates and 84 figures in the text. Cassell & Company Ltd., London, Toronto, Melbourne and Sydney. 1944. Price 16s. net.

Dr Donald Paterson's text-book, now appearing in its fifth edition, has been carefully revised and brought up to date. Its well-deserved popularity rests upon the author's extensive experience as physician and teacher, upon his vigilant scrutiny and use of recent advances in pædiatric knowledge, its comprehensive, reliable and clear presentation of the clinical problems of the healthy and sick child, and its concise instructions regarding treatment and management. The book can be recommended both for medical students in their short period of study of a large subject, and no less for medical practitioners in the responsibilities and difficulties of practice among children.

The book is well furnished with clinical, pathological and X-ray illustrations.

In its new edition it has changed its format, being now issued in a larger size of volume more convenient to hold than the previous edition.

Arthritis and Allied Conditions. By B. I. COMROE, A.B., M.D., F.A.C.P. Third Edition, Revised and Enlarged. Pp. 1359, with 329 illustrations. London: Henry Kimpton. 1944. Price 60s.

This book well merits the popularity which a third edition within five years signifies.

In addition to the most careful revision, much new material has been added, as, for example, chapters on the effect of climate on arthritis; the use of penicillin; occupational therapy; the essentials of massage; and common mistakes in arthritis and allied conditions. The book is intended both for the specialist and the general practitioner. There are chapters on specific points, written especially from the general practitioner's point of view. Perhaps the greatest value of the book is the meticulousness with which details of treatment are explained.

Any doctor who still adopts the attitude that "nothing can be done about rheumatism" should certainly read this book and he will be surprised to note that, although no major advances have been made in regard to ætiology and pathogenesis, yet there is no justification for the attitude of despair or negativism in treatment of the chronic rheumatic diseases.

Synopsis of Clinical Laboratory Methods. By W. E. BRAY, B.A., M.D. Third Edition. Pp. 528, with 93 illustrations and 20 colour plates. London: Henry Kimpton. 1944. Price 25s. net.

Advances in medical treatment and diagnosis have led to the further development of clinical laboratory methods, and many new tests are now included in the third edition of this useful synopsis.

Particular note should be made of the section on blood transfusion, where a concise account of the identification and significance of the Rh. factor is given, and a method for the demonstration of cold agglutinins is described.

Further useful material is found in the addition of liver and adrenal function tests, and the present-day importance of intestinal parasites has been stressed. This book should continue to be invaluable to the student and laboratory worker.

A Synopsis of Forensic Medicine and Toxicology. By E. W. CARYL-THOMAS, M.D., B.SC. LOND., D.P.H. Second Edition. Pp. viii+179. Bristol: John Wright & Sons Ltd. 1945. Price 10s. net.

This book deals with the duties and obligations of the medical practitioner, the ways in which he may be able to assist the law, and the procedure to be followed in giving such assistance. In such a small volume it has not been possible to deal exhaustively with all the subjects, but they are considered from the point of view of the general practitioner.

BOOKS RECEIVED

CLARK, W. E. LE GROS, F.R.S. The Tissues of the Body. An Introduction to the Study of Anatomy. Second Edition. (*Oxford University Press, London*) 21s. net.

GABRIEL, WILLIAM B., M.S., F.R.C.S. The Principles and Practice of Rectal Surgery. Third Edition . . (*H. K. Lewis & Co. Ltd., London*) 45s. net.

GURD, FRASER B., M.D., C.M., and F. DOUGLAS ACKMAN, M.D., C.M. Technique in Trauma. Planned Timing in the Treatment of Wounds including Burns. (*William Heinemann (Medical Books) Ltd., London*) 15s. net.

GUTHRIE, DOUGLAS, M.D., F.R.C.S.ED. A History of Medicine. (*Thomas Nelson & Sons Ltd., Edinburgh*) 30s. net.

HENRY, ARNOLD K., M.B., M.CH., F.R.C.S.I. Extensile Exposure Applied to Limb Surgery . . . (*E. & S. Livingstone Ltd., Edinburgh*) 30s. net.

IRONSIDE, R. N., M.B., F.R.C.P., and I. R. C. BATCHELOR, M.B. Aviation Neuro-Psychiatry . . (*E. & S. Livingstone Ltd., Edinburgh*) 8s. 6d. net.

KERSLEY, G. D., M.A., M.D., F.R.C.P. The Rheumatic Diseases. Second Edition . . (*William Heinemann (Medical Books) Ltd., London*) 15s. net.

MCLACHLAN, A. E. W., M.B., CH.B., D.P.H., F.R.S. Handbook of Diagnosis and Treatment of Venereal Diseases. Second Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 15s. net.

MUSSER, JOHN H., B.S., M.D., F.A.C.P. Internal Medicine. Its Theory and Practice . . . . . (*Henry Kimpton, London*) 50s. net.

OHNELL, RICHARD F. Pre-Excitation a Cardiac Abnormality. (*Henry Kimpton, London*) 15s. net.

Edited by TAYLOR, HOWARD C., Jr., M.D. Transactions of the American Gynecological Society. Volume 68. For the Year 1944. (*The C. V. Mosby Co., St Louis*) —

TIDY, Sir HENRY, K.B.E., M.A., M.D., and A. RENDLE SHORT, M.D., F.R.C.S. The Medical Annual. A Yearbook of Treatment and Practitioner's Index. Sixty-Third Year, 1945 (*John Wright & Sons Ltd., Bristol*) 25s. net.

Doc. Dr. W. TOMASZEWSKI. Krotki Slownik Lekarski Angielsko-Polski. Short Anglo-Polish Medical Dictionary. (*E. & S. Livingstone Ltd., Edinburgh*) 8s. 6d. net.

Edited by WAKELEY, CECIL P. G., C.B., D.SC., F.R.C.S., F.R.S.E., F.A.C.S. F.R.A.C.S.(HON.). Modern Treatment Year Book, 1945. (*The Medical Press and Circular, London*) 15s. net.

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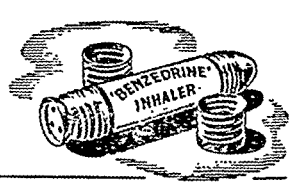

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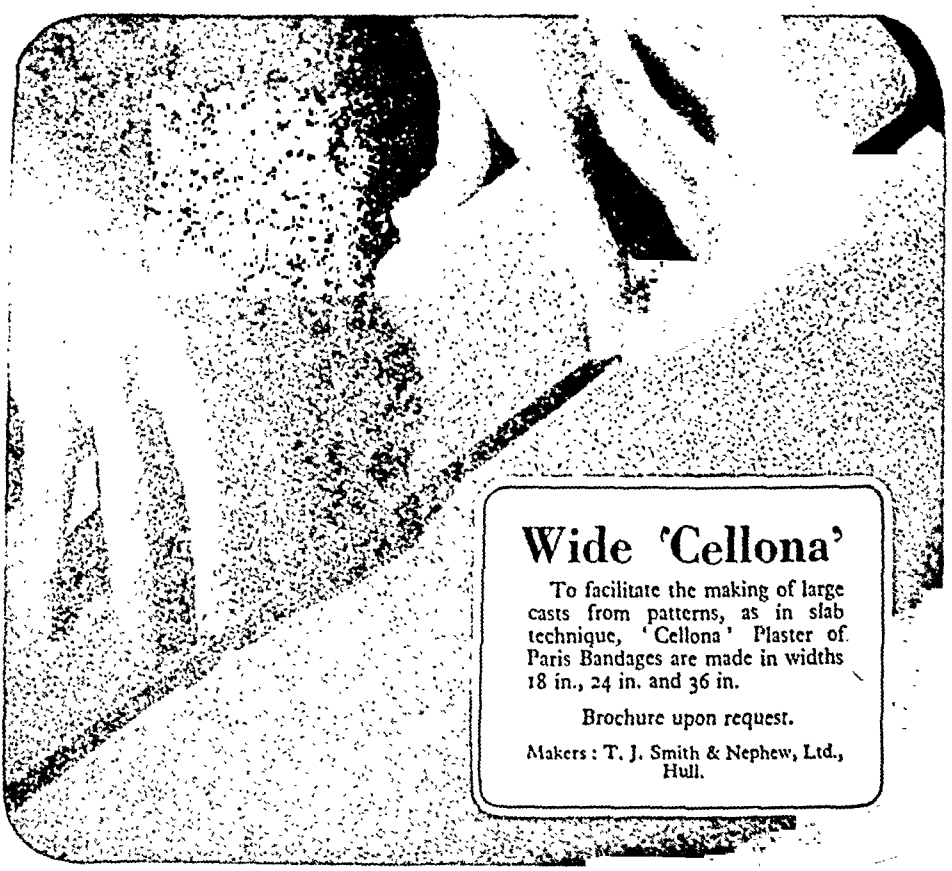

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November 1945

THE NUMBERS AND THE SITES OF ORIGIN OF THE DROPLETS EXPELLED DURING EXPIRATORY ACTIVITIES

By J. P. DUGUID, M.B., B.Sc.

From the Department of Bacteriology, Edinburgh University

INTRODUCTION

THE respiratory tract diseases, presumably spread by air-borne infection, occupy a place of predominant importance among the causes of ill-health in civilised communities. Their control remains one of the greatest of public health problems ; this has been emphasised by Wells and Wells (1936) and, more recently, by Mudd (1944), with reference to the sickness figures of the United States Public Health Service. Various measures, such as the treatment of carriers, dust-suppression and air-disinfection, have been advocated for the prevention of infective respiratory disease, but no practicable method has yet emerged which could be applied on a sufficiently large scale to ensure " safe air " for the general public. The problems of control are the more difficult because the mechanisms of air-borne infection are not yet fully understood, nor the extent known to which infection normally takes place by each of the different possible routes. For instance, the findings of some workers suggest that droplet-spray produces a heavy infection of the air which may persist for a considerable time and travel long distances (indoors), while the findings of other workers indicate that droplet-spray contains relatively few pathogenic organisms, that these are carried only in the large droplets which fall at once to the floor, and that aerial infection is caused mainly by the raising of dust which has been infected by these droplets or by more massive discharges.

Since Flugge (1897 and 1899) pointed out that a spray of small droplets may be emitted from the mouth during certain expiratory activities, much attention has been paid to droplet-spray as a means of infection. The expiratory activities which have been considered productive of droplet-spray, are sneezing, coughing, speaking, laughing and normal breathing. The significance of the part played in the spread of infection by each of these activities may be gauged according to the number of droplets which it produces and according to the frequency of its performance. Generally, it has been found that sneezing and

coughing produce many droplets, while speaking, laughing and breathing produce few. These latter activities may, however, be of considerable importance, for their performance is frequent and, moreover, they afford the only means of droplet-spray production in the case of healthy carriers, who normally neither cough nor sneeze (see Hamburger, 1944).

Various techniques have been employed for counting droplets, but no one technique is adequate to demonstrate droplets of every size, some demonstrating only the large and some only the small. Wells (1934) showed that the large droplets and the small droplets have a different ætiological significance. Droplets larger than 100 microns in diameter fall to the ground within a few seconds; droplets initially smaller than 100 microns evaporate before falling to the ground and so form residues, or "droplet-nuclei," which are small enough to remain air-borne for many hours, or even days. Thus, while the large droplets may be responsible for dust-borne infection, it is the small droplets which produce directly true air-borne infection. For this reason, counts of the large droplets and counts of the small droplets are both required for a comprehensive account of droplet-spray.

The large respiratory droplets are readily counted after collection on a slide, or on a culture plate, exposed directly in front of the mouth. The stain-marks left on the slide after evaporation of the droplets, are counted under the low power of a microscope; the colonies of commensal mouth organisms, or of *B. prodigiosus* if the mouth has been artificially infected, are counted by examination of the culture plate after incubation. These methods have been used to estimate droplet numbers by many early investigators (see Jennison, 1942), and have also been used in the present investigation. The large droplets are adequately represented in counts made in this manner, for they retain sufficient momentum to carry them out of the deflected air-stream on to the surface of the slide or plate. The smaller droplets, on the other hand, are greatly underestimated by these methods; for, on account of their small size and rapid evaporation to an even smaller size, they have little momentum and are mostly carried in the deflected air-stream past the slide or plate. Those such as Strausz (1926) who have measured the droplets collected have found that it is only droplets larger than 10 or 20 microns in diameter which are recovered on directly exposed slides. The fullest counts are obtained when the plate or slide is held close to the mouth, say within a few inches, for fewest droplets are then missed because of evaporation and scatter. In the case of vigorous sneezing, unfortunately, the plate usually becomes flooded if held close to the mouth and, consequently, application of the method is limited.

Jennison (1942) has enumerated respiratory droplets by counting the droplet images on enlarged, high-speed, dark-field photographs which were taken at the time when most droplets were present in front of the mouth. This method, like the last, demonstrates mainly the larger

droplets; it was found that only droplets with diameters over 5 or 10 microns could be clearly resolved and photographed.

The numbers of small droplets which carry commensal bacteria, may be estimated by allowing droplet-spray to become evenly distributed throughout the air of a closed chamber and then sampling a known proportion of the air for bacteria-carrying droplet-nuclei. An efficient sampling device is required, which can recover from the air on to a culture medium even the smallest bacterial particles. The slit sampler (Bourdillon, Lidwell and Thomas, 1941) appears to be the most efficient and convenient of the modern air-samplers; the authors claim for their apparatus an efficiency of over 94 per cent. in sampling the smallest bacteria-carrying particles (perhaps of only one or two microns diameter). In the present investigation the slit sampler was used for enumeration of bacteria-carrying droplet-nuclei. This method fails to demonstrate the smallest droplets, which do not contain commensal bacteria, and the droplets larger than about 100 microns in diameter, which fall at once to the ground and do not form droplet-nuclei.

In order to enumerate all the respiratory droplets small enough to form droplet-nuclei, whether or not these contained commensal bacteria, a new method was evolved and used in the present study. Stain-containing droplet-nuclei were recovered from the air on to oiled slides exposed in the slit sampler and were counted under the microscope, using oil immersion. This method demonstrated the droplets with initial diameters between about 1 and 100 microns; it gave far larger counts than were obtained by any other method.

The physical possibility of droplet-spray giving rise to air-borne infection of great extent, persistence and spread has been clearly established by the demonstration that expiratory activities may produce many droplets which are small enough to remain air-borne as droplet-nuclei. It has been found, however, by those who have investigated the expulsion of pathogenic organisms by infected persons, that aerial infection is much more limited than is suggested by the purely physical studies of droplet-spray, and that pathogenic organisms carried in the respiratory tract are not expelled as readily, nor in as great numbers, as commensal organisms from a normal mouth or *B. prodigiosus* from an artificially infected mouth (Winslow and Robinson, 1910; Bloomfield and Felty, 1924; Hare, 1940). The reason for this appears to be that the pathogenic organisms tend to be confined to certain circumscribed localities, especially to the tonsil and to the pharynx, and are seldom present at the front of the mouth, the site from which most droplets seem to originate (Bloomfield, 1921 and 1922). Thus, to assess the chances of air infection being produced by droplet-spray, information is required concerning the localities from which droplets, especially small droplets, may originate during the various expiratory activities, and also concerning the numbers of droplets which may arise from each site. The likely sites of droplet

origin are suggested by a consideration of the mechanism of atomisation and of the mechanism of each of the expiratory activities. Atomisation results from the passage of an air-stream at a sufficiently high speed over the surface of a liquid; tongues of liquid are drawn out from the surface, pulled thin and broken into columns of droplets. Air velocities high enough for atomisation are produced when the breath is forced out through some part of the respiratory tract which has been greatly narrowed. The site of narrowing, and thus of atomisation, is usually at the front of the mouth, this being almost closed by approximation of the tongue, teeth and lips. Atomisation may also perhaps occur in the throat, nearly closed by approximation of the tongue, tonsils, and soft palate; in the glottis, nearly closed by the vocal folds; in a bronchus, obstructed by secretion; in the nasal cavity, obstructed by secretion; or in the anterior nares, the narrowest parts of the normal nasal passages. In the present study the direct origin of droplets from the nose and from the throat was investigated; the number of droplets expelled from each of these sites was estimated in tests with *B. prodigiosus* applied to the site as an indicator.

Experimental Methods

The following expiratory activities were tested:—(1) normal nose-breathing for one- and five-minute periods; (2) normal mouth-breathing for a one-minute period; (3) violent simulated laughing for a one-minute period; (4) speaking loudly 100 "K's," in words such as "cake," "cook" and "kick" which contain no other consonant; (5) counting softly from "one" to "a hundred"; (6) counting loudly from "one" to "a hundred"; (7) single "throat-only coughs," voluntarily produced with mouth well open and tongue depressed; (8) single "lip-coughs," voluntarily produced with the mouth at first closed by approximation of the lips and the air blast then forced suddenly out between these; (9) single "tongue-teeth coughs," voluntarily produced with the mouth at first closed by approximation of the tongue and upper teeth and the air blast then suddenly released between these; (10) single "natural sneezes," induced by snuff or by tickling the nasal mucosa with a throat swab; (11) single "simulated sneezes," voluntarily produced by forming explosively the sound "ttsch"; and (12) single strong nasal expirations of the type made normally to clear minor obstruction or irritation. On some occasions the coughs were tested in volleys of 5 to 50 at a time and the average count calculated. Most of the tests were carried out with one subject; some were carried out with five other subjects. Between 9 and 45, and usually about 20, tests were carried out by each of the different techniques of investigation on each type of expiratory activity; the range and the arithmetic means of the counts obtained in each set of tests are given in Tables I to VI.

A. *Counts of Colonies on Culture Plates Exposed Directly to Droplet-spray*

Blood agar plates, 12 sq. in. in area, were exposed 3 in. in front of the mouth and below the nose; at this short distance, the droplet-spray was found to be scattered only to a slight extent and to fall largely within the

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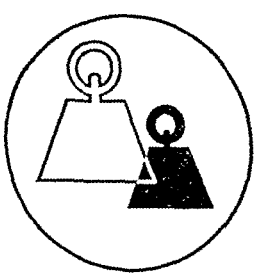

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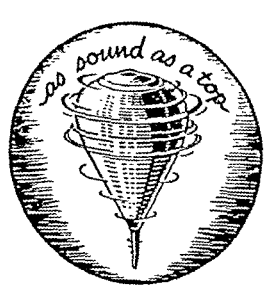

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TABLE I

Numbers of Expelled Droplets larger than about 20 microns in Diameter Revealed by Colony Counts of 12 sq. in. Blood Agar Plates Exposed 3 in. in front of the Mouth

15-45 Tests in Each Case.	Range.	Average.
Mouth breathing, 1 minute	0-0	0
Laughing loudly, 1 minute	0-6	1
Speaking loudly 100 "K's"	0-650	76
Counting softly "1"-"100"	0-30	8
Counting loudly "1"-"100"	1-284	110
"Throat-only cough"	0-1100	48
"Lip cough"	15-1344	490
"Tongue-teeth cough"	21-6500	1400
Strong nasal expiration	0-1200	280
Sneeze with mouth masked	3-185	28

TABLE II

Numbers of Expelled Droplets larger than about 20 microns in Diameter Computed from Counts of Stain-marks on Slides Exposed 6 in. in front of the Mouth

12 Tests in Each Case.	Range.	Average.
Counting loudly "1"-"100"	40-550	260
"Throat-only cough"	0-1,100	120
"Lip cough"	360-5,800	2,000
"Tongue-teeth cough"	30-7,100	1,800
Natural sneeze	3,700-46,000	24,000
Simulated sneeze (weak)	5,000-52,000	26,000

TABLE III

Numbers of Bacteria-carrying Droplets initially smaller than about 100 microns in Diameter Computed from Colony Counts of Blood Agar Plates Exposed in the Slit Sampler between Half and One and a Half Minutes after Droplet-Spray Production

9-23 Tests in Each Case.	Range.	Average.
Strong nasal expiration	0-65	16
Speaking loudly 100 "K's"	0-30	7
Counting softly "1"-"100"	0-35	13
Counting loudly "1"-"100"	5-210	71
"Throat-only cough"	0-80	8
"Lip cough"	5-3,500	720
"Tongue-teeth cough"	80-1,500	730
Natural sneeze	4,500-150,000	39,000
Simulated sneeze (strong)	120,000-1,000,000	310,000

TABLE IV

Numbers of Expelled Droplets with Initial Diameters between about 1 *and* 100 *Microns Computed from Counts of Stain-containing Droplet-nuclei on Oiled Slides Exposed in the Slit Sampler between Half and One and a Half Minutes after Droplet-spray Production*

16-20 Tests in Each Case.	Range.	Average.
Counting softly "1"-"100"	0-160	63
Counting loudly "1"-"100"	50-770	250
"Lip cough"	490-16,000	4,800
"Tongue-teeth cough"	1,500-52,000	8,200
Natural sneeze	65,000-3,100,000	1,100,000
Simulated sneeze (strong)	1,500,000-30,000,000	9,300,000

TABLE V

Numbers of Expelled Droplets larger than about 20 *Microns in Diameter originating from* (1) *the Throat and* (2) *the Nose, as Revealed by Counts of* B. prodigiosus *Colonies on* 12 *sq. in. Plates Exposed* 3 *in. in front of Mouth and Nose*

	15-30 Tests in each case.	Range.	Average.
From throat	Laughing loudly, 1 minute	0-12	2
	Speaking loudly 100 "K's"	0-1100	92
	"Throat-only cough"	0-279	31
	Natural sneeze	0-2300	360
From nose	Nose breathing, 5 minutes	0-6	2
	Natural sneeze	0-5600	250

TABLE VI

Numbers of Expelled Droplets initially smaller than about 100 *Microns in Diameter originating from* (1) *the Throat and* (2) *the Nose, as Computed from Counts of* B. prodigiosus *Colonies on Plates Exposed in the Slit Sampler between Half and One and a half Minutes after Droplet-spray Production*

	10 Tests in Each Case.	Range.	Average.
From throat	Speaking loudly 100 "K's"	0-33	7
	"Throat-only cough"	0·2-5·3	2
	Natural sneeze	0-390	110
From nose	Nose breathing, 5 minutes	0-5	2
	Natural sneeze	5-360	56

area covered by the plate. After aerobic incubation for forty-eight hours the colonies were counted with the aid of a plate microscope. When the culture plate had been exposed only momentarily, as in the test of a cough, it was assumed that all the colonies found had resulted from the impingement of droplets. When, however, the plate had been exposed for a longer period, as in tests of speaking or breathing for one minute, there was the possibility

that some of the colonies had resulted from the deposition on the plate of airborne dust organisms. The number of such contaminants found on control plates exposed behind the head for a one-minute period varied between 5 and 20. The contaminants were mostly staphylococci and sarcinæ, and never *Str. viridans*. In contrast, the majority (50 to 80 per cent.) of the colonies resulting from mouth-spray contained *Str. viridans*. Accordingly, in tests where the culture plate was exposed for a one-minute period, only the *Str. viridans* colonies were counted, this organism being taken as evidence of mouth-spray origin. In tests of nose-breathing no such procedure was possible, for the nose-spray organisms usually resembled the aerial flora. In Table I are summarised the results obtained by this method.

B. *Counts with the Microscope of Droplet Marks on Slides Exposed Directly to Mouth-spray*

To ensure that even the smallest droplet marks would show distinctly, a little powdered congo red, eosin or fluorescein was applied with a throat swab to the surfaces of the mouth and fauces, especially to the lips, front teeth and tip of tongue. After the dye had dissolved in the oral secretions, droplet-spray was directed towards slides held 6 in. in front of the mouth. The number of droplet marks in 1 sq. in. of the slide was counted under the low power of the microscope. In other tests the area of cross-section of the droplet-spray at 6 in. in front of the mouth was ascertained approximately from measurements of the area of intense staining on paper grids held in place of the slides. The average area for 6 sneezes was 20 sq. in., and for 12 coughs was 10 sq. in. The number of sneeze droplets found per square inch was therefore multiplied by 20, and the number of cough droplets per square inch by 10. The results obtained by this method are summarised in Table II. A large number of the droplet stain-marks were measured under the microscope with a micrometer eyepiece and the sizes of the parent droplets were calculated by making allowance for the flattening which took place on impingement upon the slide; some droplets of only 5 microns in diameter, and many of 10 microns, were found to have impinged; it appeared, however, that only droplets larger than about 20 microns in diameter were adequately represented in counts by this method.

C. *Counts of Colonies on Culture Plates Exposed in the Slit Sampler*

Tests were carried out by the same general method as employed by Bourdillon, Lidwell and Lovelock (1942). Three closed chambers were used, of 1700 cub. ft., 70 cub. ft., and $2\frac{1}{2}$ cub. ft. respectively. In the case of the two larger chambers, an electric fan was run at half speed to ensure thorough distribution of the droplet-nuclei; droplet-spray was directed forwards into the air-stream from standing height (5 ft.); the air was sampled through an intake 3 ft. 4 in. above the floor. In the case of the $2\frac{1}{2}$ cub. ft. box, droplet-spray was introduced horizontally through a face-hole $1\frac{1}{2}$ ft. above the floor of the box; air was sampled through an intake at the level of the floor. In tests of sneezing it was most convenient to use the larger chambers and so obtain considerable dilution of the very numerous droplets; in tests of coughing and speaking it was most convenient to use the small chambers and so maintain as high a concentration as possible of the less

numerous droplets. Because of the shorter falling distance, some droplets which would have had time to evaporate in the larger chambers must have failed to become droplet-nuclei in the 2½ cub. ft. box. These, however, were apparently but a small proportion of the whole, for the average counts obtained in the different chambers were very similar; no distinction has been drawn between the different chambers in recording the results in this paper. After the production of the droplet-spray, half a minute was allowed for the formation and distribution of the droplet-nuclei; during the minute following this, 1 cub. ft. of air was sampled on to a blood agar plate exposed in the slit sampler. The plate was incubated aerobically for forty-eight hours, the colonies were counted with the aid of a plate microscope, and the total number of droplet-nuclei was computed from this count minus the "control count" of air-borne dust organisms. The "control counts" were obtained from samples taken just before droplet-spray production; usually from 5 to 10 colonies of staphylococci and sarcinæ were found on 1 cub. ft. control plates, while *Str. viridans* was very seldom found. In tests of speaking and coughing the "test count" was often very little greater than the "control count"; when the "test count" was less than 40, only the number of *Str. viridans* colonies was recorded, the presence of this organism being taken as evidence of mouth-spray origin. In Table III are summarised the results obtained by this method.

D. *Counts with the Microscope of Stain-containing Droplet-nuclei on Oiled Slides Exposed in the Slit Sampler*

If the droplet-nuclei, especially the smaller ones, are to be readily recognised amid other particles of air-borne dust, it is necessary that they should be brightly coloured by some dye previously taken into the mouth. Just prior to each test a little powdered congo red was applied with a throat swab to the surfaces of the mouth and fauces, especially to the front teeth, lips and tip of tongue. Sometimes the dye induced excessive salivation; if so, the extra saliva was swallowed. Mouth-spray was produced in one or other of the three chambers described above. Half a minute was allowed for the formation and distribution of the droplet-nuclei. During the minute following this, 1 cub. ft. of air was sampled with the slit sampler; if the droplet-nuclei were very numerous, only ½ cub. ft., or even less, was sampled. Instead of using a culture plate in the slit sampler, a microscope slide, previously spread thinly with a 5 per cent. solution of boiled linseed oil in chloroform, was placed on the platform 2 mm. below the "slit." The platform was not rotated; accordingly, the air-dust and droplet-nuclei were deposited on the slide in a thin, easily visible line. This line, the "dust-line," was 29 mm. long; its width was indefinite, for although most of the particles were concentrated in a central strip ½ mm. wide, a few were scattered for distances up to 1 mm on either side. A drop of immersion oil was placed directly on the dust-line and this was examined with a microscope, using a mechanical stage, a $\frac{1}{12}$ in. objective and a (×8) eyepiece with a micrometer scale set in it. The scale, which had 10 major and 100 minor divisions, represented in all a length of 170 microns on the dust-line. In the search for droplet-nuclei the dust-line was scanned in transverse bands, each of which was 170 microns of its length. This was conveniently done by setting the micrometer scale parallel to the dust-line and moving the slide so that the dust-line passed under the scale from side to side; all the droplet-nuclei in the band were counted as they

passed the scale (see Fig.). The search was continued in transverse bands selected at intervals along the length of the dust-line until an adequate number of nuclei had been counted, usually from 300 to 500. If the nuclei were scanty, the whole dust-line might have to be searched before the count of even a few dozen could be obtained. If the nuclei were numerous, only 10, 20 or 30 transverse bands of 170 microns width were scanned. If the nuclei were very numerous, narrow transverse bands were examined; these occupied only 34 microns of the length of the dust-line and were covered by the two central major divisions of the scale. By appropriate multiplication, the number of nuclei in the whole dust-line (*i.e.* in $\frac{1}{2}$ or 1 cub. ft. of air) and then the number in the total volume of the chamber, was calculated. As the initial counts were subject to the standard error of random sampling and as the computation usually involved a big multiplication (*e.g.* by 3500 in the computation for a sneeze and by 10 in the computation for a cough in the 70 cub. ft. chamber), the accuracy of the final figures obtained is not high; it is, however, the approximate number of the expelled droplets, rather than

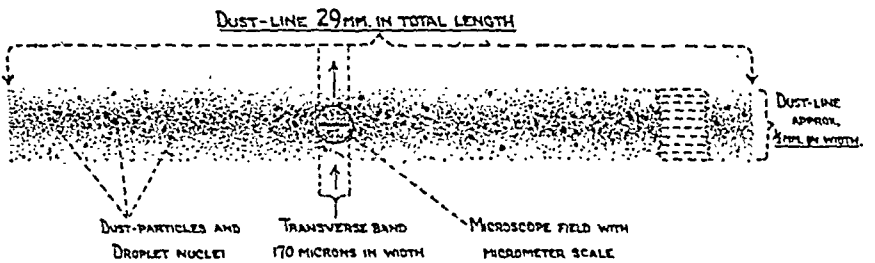

FIG.—Showing how the dust-line is scanned from side to side in transverse bands as these are passed under the micrometer scale.

the exact number, which is of interest. In recording the results, the counts are given corrected to two significant figures; this is not to be taken as an indication of the degree of their accuracy (Table IV).

The droplet-nuclei were readily distinguished from the black-green dust particles by their bright red colour. Most were spherical in shape, sometimes regular but more often irregular with indentations and ridges; a considerable number were disc-shaped or spindle-shaped. The nuclei recovered in the tests in the larger chambers were mostly between 0·25 and 25 microns in diameter; those recovered in the tests in the $2\frac{1}{2}$ cub. ft. box were mostly between 0·25 and 15 microns in diameter; the commonest diameter in each case was between 1 and 2 microns. It was uncertain whether or not there was any considerable number of small nuclei which, on account of their smallness, were not recovered by the slit sampler or not recognised under the microscope. It was found by microscopic observation of the evaporation of large droplets of stain-containing saliva that a droplet-nucleus had a diameter about one quarter that of its parent droplet. It appears, therefore, that the counts obtained by this technique represent the expelled droplets with initial diameters between about 1 and 100 microns. These counts (Table IV) were much higher than the counts obtained for bacteria-carrying droplets small enough to form droplet-nuclei (Table III). The probable reason for this is that many of the smaller droplets do not contain bacteria and are thus not

demonstrated by the culture method. The preponderance was greatest in the case of the most violent expiratory activities; it was, on average, about thirty-fold for sneezing, ten-fold for coughing and five-fold for speaking.

E. *Counts of Droplets Originating from the Throat and from the Nose*

A throat swab was rubbed in a surface growth of *B. prodigiosus* and was applied, just before the test, to the throat or to the nose. For investigation of throat origin, only the tonsillar region, the free edge of the soft palate and the back of the tongue were inoculated; the anterior mouth was then proved free of *B. prodigiosus* by a swab taken from the front teeth, lips and tip of tongue. For investigation of nasal origin, the anterior nares and forward parts of the nasal cavities were inoculated. The numbers of *B. prodigiosus*-containing droplets which were expelled during the different expiratory activities, were assessed both by the method of counting colonies on directly exposed culture plates and by counting colonies on plates exposed in the slit sampler. The results obtained are summarised in Tables V and VI.

Discussion of Results

Normal Breathing.—It was early realised (Tyndall; Nageli; Buchner; Werrich; see Chapin, 1912) that bacteria are not liberated spontaneously from undisturbed moist surfaces, such as those of the respiratory tract at rest. Normally expired breath has usually been found to be free of organisms; Tyndall found the breath of normal persons to be devoid of germs; Flugge, Cadeac and others could not demonstrate tubercle bacilli in the normally expired breath of consumptives. Koelzer (see Wood, 1905), on the other hand, suggested that atomisation might occur within a tuberculous lung during normal respiration and that the breath might contain a few infected droplets. Meleney (1927) suggested that organisms might be expelled from the nose during normal expiration, perhaps being blown off hairs in the nostrils. The personnel of Naval Laboratory Research Unit No. 1 (1943), in a recent review of air-borne infection, included normal breathing among the air-infecting mechanisms.

In the present investigation no droplets were found to be expelled by *normal mouth-breathing for a one-minute period* in any of 15 tests with directly exposed culture plates. *Normal nose-breathing for a five-minute period* was, on the other hand, found usually to result in the expulsion of a few droplets, which originated from the nose; "large" droplets of over about 20 microns diameter, numbering from 1 to 6, were found to be expelled in 19 out of 30 tests with directly exposed plates; bacteria-carrying droplet-nuclei, numbering from 1 to 5, were found to be expelled in 7 out of 10 tests with the slit sampler. It appears then that infected droplets may be introduced into the air by breathing. The number of these droplets is small; yet, if two droplets are expelled every five minutes, the daily total of about 500 is not negligible.

If nasal expiration is somewhat more forceful, as in the effort to clear minor obstruction or irritation, many more droplets may be expelled. In 15 tests with directly exposed plates the number of "large" droplets found to be expelled by a *strong nasal expiration* varied from 0 to 1200 (on average, 280). In 9 tests with the slit sampler, the number of bacteria-carrying droplet-nuclei found to be produced by a *strong nasal expiration* varied from 0 to 65 (on average, 16).

Laughing.—Although seldom considered of importance, recent mention has been made of laughing, as a possible cause of droplet emission, by Hamburger (1944) and Mitman (1945). In the present investigation *violent simulated laughing for a one-minute period* was found to produce a few "large" droplets, numbering from 1 to 12, in 14 out of 30 tests with directly exposed plates. In 15 of the tests, *B. prodigiosus* was used as an indicator of throat origin, and in 8 out of these 15 tests the few droplets expelled were shown to have originated from the throat. Because of the few droplets produced and because of the infrequency of prolonged laughing, it is unlikely that laughing plays any significant part in the spread of infection.

Speaking.—The findings of the investigators who have used directly exposed plates for the enumeration of droplets, have been summarised by Jennison (1942); typically, from a few to a few hundred droplets were obtained from a few minutes' speaking. In photographic studies, Jennison (1942) found the number of droplets produced by each word or consonant to vary from a few dozen in normal conversation to a few hundred in loud talking.

In the present investigation the number of "large" droplets found to be expelled in *counting softly from "one" to "a hundred"* varied in 15 tests with directly exposed plates and slides from 0 to 30 (on average, 8); the number expelled in *counting loudly from "one" to "a hundred"* varied in 27 tests from 1 to 550 (on average, 180). The numbers of droplets small enough to remain air-borne as droplet-nuclei were found in tests with the slit sampler to be as great or greater. The number of bacteria-carrying droplet-nuclei produced by *counting softly* varied in 23 tests from 0 to 35 (on average, 13); the number produced by *counting loudly* varied in 23 tests from 5 to 210 (on average, 71). The number of microscopically visible droplet-nuclei produced by *counting softly* varied in 20 tests from 0 to 160 (on average, 63); the number produced by *counting loudly* varied in 20 tests from 50 to 770 (on average, 250).

In speaking, expiration is intermittently checked by the enunciation of consonants; these involve closures or narrowings of the air-way, thereby causing locally high air-speeds and atomisation. Koeniger (see Wood, 1905) found that most droplets were produced by the letters "P," "T," "F," and "K." Jennison (1942) found that most droplets were expelled in the enunciation of "P," "T," "F," and "S." In *counting from "one" to "a hundred,"* as in the present study, the most frequent droplet-producing consonants are "T," "F" and "S";

in the case of these, the closure, and thus atomisation, occur at the front of the mouth. For this reason, the numbers obtained in tests of counting must refer to droplets originating from the anterior mouth. On the other hand, it is probable that droplets emitted in the enunciation of words containing " K " as the sole consonant, originate from the throat where the closure and highest air-speeds presumably occur. The number of " large " droplets expelled by *speaking loudly* 100 " *K's* " was found in 30 tests with directly exposed plates to vary from 0 to 1100 (on average, 84), no droplets being expelled in 9 out of the 30 tests. The number of bacteria-carrying droplet-nuclei produced by *speaking loudly* 100 " *K's* " was found in 19 tests with the slit sampler to vary from 0 to 33 (on average, 7), no bacterial nuclei being produced in 7 out of the 19 tests. In 25 of the tests, *B. prodigiosus* was used as an indicator of throat origin and in 18 out of these 25 tests the droplets expelled were shown to have originated from the throat. In normal conversation, loudly enunciated " K's " are not very frequent; most droplets expelled in speaking must originate from the anterior mouth and very few from the throat.

Coughing.—The findings of the investigators who used directly exposed plates to enumerate droplets, have been summarised by Jennison (1942); typically, a cough was found to produce from a few to a few hundred droplets. In photographic studies, Jennison (1942) obtained from a few dozen to a few hundred droplets for each cough.

In the present investigation it was found that when a cough was performed with the mouth kept well open and the tongue depressed (" *throat-only cough* "), few or no droplets were expelled; when, on the other hand, the mouth was closed at the start of the cough, either by approximation of the lips (" *lip cough* ") or by approximation of the tongue and teeth (" *tongue-teeth cough* "), many droplets were expelled. The number of " large " droplets found in 57 tests with directly exposed plates and slides to be expelled by a single " *throat-only cough* " varied from 0 to 1100 (on average, 63), no droplets being expelled in 19 out of the 57 tests; the number expelled by a single " *lip cough* " varied in 27 tests from 15 to 5800 (on average, 1200); the number expelled by a single " *tongue-teeth cough* " varied in 27 tests from 21 to 7100 (on average, 1600). In tests with the slit sampler, droplets small enough to remain air-borne as droplet-nuclei were demonstrated; in the case of coughs performed with the mouth initially closed, these small droplets were found to be very numerous. The number of bacteria-carrying droplet-nuclei produced by a single cough varied in 21 tests of a " *throat-only cough* " from 0 to 80 (on average, 8), in 19 tests of a " *lip-cough* " from 5 to 3500 (on average, 720) and in 19 tests of a " *tongue-teeth cough* " from 80 to 1500 (on average, 730). The number of microscopically visible droplet-nuclei produced by a single cough varied in 16 tests of a " *lip cough* " from 490 to 16,000 (on average, 4800) and in 16 tests of a " *tongue-teeth cough* " from 1500 to 52,000 (on average, 8200).

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Jennison (1942) suggested that, in coughing, the majority of the droplets may originate from the pharyngeal region instead of from the front of the mouth, as in speaking and sneezing; the mouth often remains well open during a cough and in such cases the highest air-speed, and probably also the zone of greatest droplet formation, must occur in the pharyngeal region. The findings of Bloomfield and Felty (1924) suggest that this is not the case; these workers inoculated the tonsils of three subjects with a culture of *B. coli* and subsequently exposed culture plates a few inches in front of the mouth during coughing; no droplets containing *B. coli* were expelled by any of the subjects. In the present investigation similar tests were carried out with *B. prodigiosus* applied to the tonsillar region of the subject; the expulsion of droplets containing this organism was demonstrated in 37 out of 40 tests of a single "*throat-only cough*." The number of "large" droplets expelled from the throat in a cough was found in 30 tests with directly exposed plates to vary from 0 to 279 (on average, 31). The number of bacteria-carrying droplet-nuclei originating from the throat in a cough was found in 10 tests with the slit sampler to vary from 0·2 to 5·3 (on average, 2). The difference between these results and the findings of Bloomfield and Felty may perhaps be due to more vigorous coughing in the present investigation or to more liberal and more widespread inoculation of the indicator organism, all regions of the posterior mouth and fauces being inoculated instead of the tonsillar area alone.

Ziesché (1907) examined microscopically the droplets caught on slides exposed to the coughing of subjects with open pulmonary tuberculosis. On the basis of morphological differences described by Heymann (1899), he distinguished droplets of bronchial origin, containing thick mucus, leucocytes and tubercle bacilli, from droplets of oral origin, containing thin mucus, epithelial cells, commensal mouth organisms, but no, or occasionally a few, tubercle bacilli. He found that the bronchial droplets were usually less numerous than the oral droplets and that they were less frequently produced. If a bronchus is obstructed by exudate, the air velocity presumably may become sufficiently raised to cause atomisation; in this way infection may be introduced directly into the air from a diseased lung. It seems likely, however, that most droplets originating in a bronchus will impinge upon the walls of the respiratory tract higher up and so fail to pass out of the mouth. The organisms of lung infections may more commonly be expelled in droplets of bronchial exudate which has been first coughed up into the throat or mouth and then atomised from one of these sites.

Sneezing.—Much larger numbers of droplets are produced in sneezing than in coughing and speaking. Wells (1935) found that a sneeze produced over 20,000 bacteria-carrying droplet-nuclei. Bourdillon and Lidwell (1941) obtained 19,000 colonies on a 60 sq. in. serum-agar plate exposed 3 feet in front of the mouth during a sneeze.

Bourdillon, Lidwell and Lovelock (1942) found that snuff-induced sneezes each gave rise to about 100,000 bacteria-carrying droplets small enough to remain air-borne as droplet-nuclei for at least one minute. Jennison (1942), in photographic studies, found that the droplets expelled during a sneeze numbered in many cases about 20,000; he quoted 40,000 as a high count and 4500 as a low count.

In the present investigation the number of "large" droplets expelled by a single "*natural sneeze*" was found in 6 tests with directly exposed slides to vary from 3700 to 46,000 (on average, 24,000). Results similar to those of Bourdillon, Lidwell and Lovelock were obtained in tests carried out by their method using the slit sampler. The number of bacteria-carrying droplets small enough to remain air-borne for at least half a minute, which were produced by a single "*natural sneeze*," was found in 21 tests to vary from 4500 to 150,000 (on average 39,000). The numbers of droplet-nuclei found by microscopic examination of slides exposed in the slit sampler were much greater; they varied in 18 tests from 65,000 to 3,100,000 (on average, 1,100,000) per single "*natural sneeze*." "*Violent simulated sneezes*" were found to produce more droplets than "*natural sneezes*"; the number of bacteria-carrying droplet-nuclei produced by a "*violent simulated sneeze*" varied in 23 tests from 120,000 to 1,000,000 (on average, 310,000); the number of microscopically visible droplet-nuclei varied in 18 tests from 1,500,000 to 30,000,000 (on average, 9,300,000).

In the expiratory phase of a sneeze, some air passes out through the nose but most escapes through the mouth, rushing at maximum speed between the approximated teeth; it is chiefly the secretions of the anterior mouth about the front teeth which are atomised. In photographic studies, Jennison (1942) found that most sneeze droplets appeared to originate from the front of the mouth and that, in both stifled and unstifled sneezes, relatively few, if any, droplets issued from the nose; the nasal exudate was often expelled as large masses rather than as small droplets. Bourdillon and Lidwell (1941), also in photographic studies, found that although the majority of droplets usually came from the mouth, in some sneezes there was a purely nasal discharge, albeit slight, and in others a mixed oral and nasal discharge. In the present investigation the numbers of droplets emitted from the nose during sneezing were estimated in tests with the mouth efficiently masked with an impermeable shield and in tests with *B. prodigiosus* applied to the anterior nares and anterior nasal cavity. The number of "large" droplets expelled by a single "*natural sneeze*" was found in 40 tests with directly exposed plates to vary from 0 to 5600 (on average, 190), no droplets being expelled in 4 out of the 40 tests. The number of bacteria-carrying droplet-nuclei originating from the nose in a single "*natural sneeze*" was found in 10 tests with the slit sampler to vary from 5 to 360 (on average, 56). It appears then that sneezing may give rise to a small amount of air-borne infection with nose-carried organisms.

Bloomfield and Felty (1924) found that droplets were not readily expelled from the throat during sneezing; no droplets containing *B. coli* were expelled during sneezing by any of three subjects to whose tonsillar regions a culture of *B. coli* had been applied. In the present investigation droplets were found to be expelled from the throat by a single "*natural sneeze*" in 20 out of 25 tests with *B. prodigiosus* used as an indicator of throat origin. The number of "large" droplets originating from the throat was found in 15 tests with directly exposed plates to vary from 0 to 2300 (on average, 360) per sneeze. The number of bacteria-carrying droplet-nuclei originating from the throat was found in 10 tests with the slit sampler to vary from 0 to 390 (on average, 110) per sneeze. It appears then that sneezing may produce a small amount of air-borne infection with organisms carried only in the faucial region.

Conclusions

Speaking, coughing and sneezing produce very many droplets small enough to remain air-borne as droplet-nuclei. Nearly all of these small droplets originate from the front of the mouth; only relatively few, if any, originate from the nose, as in sneezing and breathing, or from the throat, as in sneezing, coughing, speaking and laughing. The extent of the air-borne infection which may be produced by the droplet-spray of infected persons must depend, therefore, largely upon the frequency with which pathogenic organisms, especially large numbers of these, are present in the secretions of the anterior mouth; this frequency, according to the little information available, does not appear to be great. The hazard of air infection with droplets originating from the nose or from the throat, sites in which pathogenic organisms are often carried and often numerous, is limited by the small amount of atomisation which takes place at these sites. To decide the part played by droplet-spray in the spread of infection, more information is needed about the occurrence in the anterior mouth secretions of the different pathogenic organisms and also about the numbers of expelled droplets, especially small droplets, which may contain these pathogenic organisms.

Summary

(1) The numbers of droplets expelled during normal breathing, strong nasal expiration, laughing, speaking, coughing and sneezing, have been estimated by four different methods: (i) counting colonies on culture plates exposed directly to droplet-spray: this gives the numbers of bacteria-carrying droplets larger than about 20 microns in diameter; (ii) counting droplet stain-marks on slides exposed directly to droplet-spray: this gives the numbers of all droplets larger than about 20 microns in diameter; (iii) counting colonies on culture plates exposed in the Bourdillon slit sampler: this gives the numbers

of bacteria-carrying droplets small enough, with initial diameters under about 100 microns, to remain air-borne as droplet-nuclei; (iv) counting all microscopically visible droplet-nuclei found on oiled slides exposed in the slit sampler, the nuclei being coloured by dye previously taken into the mouth; this is a new method and it gives the numbers of droplets with initial diameters between about 1 and 100 microns; these counts are considerably greater than the counts obtained by any other method.

(2) The numbers of droplets originating from the nose and from the throat were estimated in tests with *B. prodigiosus* inoculated as an indicator on to one of the sites.

(3) Normal breathing for a five-minute period sometimes did not produce any droplets and sometimes produced a few; these were found to originate from the nose. A single strong nasal expiration produced from a few to a few hundred droplets; some of these were small enough to form droplet-nuclei.

(4) Laughing for a one-minute period sometimes did not produce any droplets and sometimes produced a few; these were found to originate from the faucial region.

(5) Counting softly from "one" to "a hundred" produced from a few to a few dozen droplets; counting loudly from "one" to "a hundred" produced from a few dozen to a few hundred; these apparently originated from the front of the mouth and most were small enough to form droplet-nuclei. Enunciating loudly 100 "K's" sometimes did not produce any droplets and sometimes produced a few dozen or a few hundred; many of these droplets originated from the faucial region and a few of the faucial droplets were small enough to form droplet-nuclei.

(6) A single cough with the mouth kept well open sometimes did not produce any droplets and sometimes produced a few dozen or a few hundred; it was found that many of these droplets originated from the faucial region and that a few of the faucial droplets were small enough to form droplet-nuclei. A single cough with the mouth initially closed produced from a few hundred to many thousand droplets; these apparently originated from the front of the mouth and most were small enough to form droplet-nuclei.

(7) A single natural sneeze produced from a few hundred thousand to a few million droplets; these apparently originated from the front of the mouth and most were small enough to form droplet-nuclei. In most sneezes, between a few and a few thousand droplets were found to originate both from the nose and from the faucial region; some of these droplets arising from the nose and throat were small enough to form droplet-nuclei.

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WAR WOUNDS AND INJURIES INVOLVING THE PARANASAL AIR SINUSES

By R. B. LUMSDEN, M.B., F.R.C.S.Ed., Lieutenant-Colonel, R.A.M.C., Adviser in Oto-Rhino-Laryngology to M.E.F.

THE object of this paper is to record a series of 20 cases, to indicate the problem which they presented, and to discuss methods of treatment. Wound excision, cleansing of the opened paranasal air sinus and suture with or without drainage is in some cases no less successful than in wounds not involving an air sinus. The fact that a wound has involved an air sinus, particularly one which has involved the fronto-ethmoidal region, has generally rightly to be regarded *per se* as of secondary immediate importance compared with the frequent co-existent damage to other structures and the very great risk of spread of infection intracranially. Of the 20 cases recorded below, all but one (Case 15) had previously come under the care of a neuro-surgeon, an ophthalmologist or a maxillo-facial surgeon. Frontal or fronto-ethmoidal sinus involvement occurred in 9 cases; maxillary or maxillo-ethmoidal sinus involvement occurred in 11. There was one death in the latter group (Case 19).

FRONTAL AND FRONTO-ETHMOIDAL SINUS CASES

Seven of the 9 cases were battle casualties while 2 were due to blunt injury. The operations which were carried out followed well-recognised methods which can be classified under three headings: (1) external ethmoidectomy, (2) external operation to establish frontal sinus drainage into the nose (Howarth's operation), (3) complete frontal sinus obliteration.

CASE 1. Tpr. T. Aged 27. Penetrating shell wound of left orbit and ethmoidal sinuses. External ethmoid operation:—On 1st November 1942 this soldier was hit by a piece of metal 2·5×1×0·5 cm., which entered the left orbit and destroyed the left eye. Thirty-six hours later the eye was eviscerated in the forward area. Three days after being wounded he arrived at a general hospital and was admitted to the ophthalmic department with a ragged, infected wound of the left upper eyelid. On X-ray examination, a metallic foreign body was found to have passed through the left orbit and ethmoid and was lying in the right pterygoid region. Six days after admission, the nose was examined. On the left side there was blood-clot and necrotic tissue, and the posterior part of the vomer was found lying free in the posterior region of the right nasal cavity. This was easily extracted through the nose. Posterior rhinoscopy revealed an area of ulceration of the right side of the nasopharynx and upper surface of the palate, which healed rapidly. Exploration failed to locate the piece of metal, which was left *in situ*. Twelve days after being wounded he commenced to have pain, tenderness and swelling

TABLE I

Frontal and Fronto-Ethmoidal Sinus Cases

Case.	Nature of Injury.	Interval between Injury and First Operation.	Nature of First Operation.	Late Clinical Features.	Nature of Subsequent Operation.	Interval between Injury and Subsequent Operation.	Findings at Subsequent Operation.	Result.
1. Tpr. T.	Shell wound of left orbit and ethmoid	36 hours	Evisceration of left eye	Pain, tenderness, swelling of supero-medial orbital region	Left external ethmoidectomy	17 days	Bone fragments, pus	Healed by first intention
2. Tpr. D.	Injury of supero-medial aspect of left orbit with comminuted fracture of orbit, involving frontal and ethmoid	12 hours	Wound trimmed and sutured	Primary healing followed by breaking down of wound. Polypi in nose. (Pre-existing sinusitis probable)	Left external frontal drainage (Howarth)	6 weeks	Some fragments in frontal and ethmoid. Pus in frontal, ethmoid, sphenoid and both antra. Polypi in ethmoid	Healed in twelve days
3. Sgt. A.	Shell wound involving left orbit and both frontals, with dural involvement	18 hours	Enucleation of left eye and debridement of frontal wound	Persistent discharge from fistula in frontal region	Bilateral frontal obliteration	5 months	Bone fragments, pus, polypoid mucosa. Extensive bone loss. Exposed, scarred dura	Healed in four weeks (post-traumatic epilepsy)
4. Sgt. R.	Bomb wound involving both frontals	24 hours	Wound trimmed, bone fragments removed	Persistent discharge from frontal fistula	Right frontal obliteration. Left frontal drainage (Howarth)	7 weeks	Pus, polypoid mucosa	Healed in three weeks
5. Spr. R.	Shell wound involving both frontals, with dural penetration	27 days	Frontal sinus "unroofed"	Discharge from large defect in frontal region	Bilateral frontal obliteration	2½ months	Bone fragments, pus, polypoid mucosa. Exposed scarred dura	Not known. (Scalp defect on invaliding)
6. Lt. T.	Shell wound involving left frontal and ethmoid	About 24 hours	Metallic F.B. removed from ethmoid region. Depressed anterior frontal wall elevated. Wound excised and closed	Wound broken down and discharging	Left frontal obliteration	3 weeks	Bone fragments, pus	Not known. (Clean fronto-ethmoidal fistula on invaliding)
7. L/Cpl. E.	Bomb wound left orbit, nose and left frontal, with dural involvement	About 24 hours	Wound trimmed and left eye eviscerated	Persistent discharge from frontal fistula. (Also independent nasal fistula)	Left frontal obliteration	6 months	Pus, polypoid mucosa. Extensive bone loss. Exposed, grossly scarred dura	Wound healed in three weeks. Subsequent plastic closure of nasal fistula
8. Gnr. F.	Shell wound involving both frontals, with dural involvement	About 30 hours	Wound excised and bone defect enlarged. Bone fragments removed. Depressed inner sinus wall elevated. Wound not sutured	Discharge from fistula in frontal region. Metallic F.B. present	Exploration of right frontal. Wound sutured with drainage	9 days	Bone fragments. Metallic F.B. in fronto-nasal duct	Healed in ten weeks. (Late operative treatment withheld in view of result of lipiodol investigation)
9. L/Cpl. S.	Compound, depressed fracture of left frontal	3 hours	Wound excised. Bone defect enlarged and fragments removed from sinus. Sutured with drainage	Persistent discharge from fistula in frontal region	Wound re-opened and sinus drained	3 weeks	...	Healed in four months. (Late operative treatment withheld in view of result of lipiodol investigation)

of the supero-medial orbital region. The C.S.F. was normal. X-ray showed obscurity of the left ethmoidal sinuses, the other sinuses being normally translucent. His condition did not improve, and on 18th November (seventeen days after being wounded) an operation was carried out through a curved incision commencing over the supra-orbital margin and carried medial to the inner canthus along the side of the nose. On elevating the orbital periosteum the orbital roof, *i.e.* the floor of the frontal sinus was found to be intact. The medial orbital wall, *i.e.* the lamina papyracea of the ethmoid was found to have been shattered and the ethmoidal air cells contained multiple bone fragments and pus. The ethmoidal air cells were completely exenterated, and the fronto-nasal duct was enlarged by removing a portion of the frontal process of the maxilla. The frontal sinus itself was *not* opened. Its lining mucosa in the region of the duct was seen to be healthy. A large firm-walled rubber drainage tube was inserted with its upper end lying at the entrance to the frontal sinus, its lower end extending to the external naris. The external wound was sutured without drainage and healed by first intention. Plastic repair of the upper eyelid was subsequently carried out. The patient was seen in June 1944. He had remained fit since his discharge from hospital.

CASE 2. Tpr. D. Aged 24. Injury of supero-medial aspect of left orbit, with comminuted fracture of the orbit, involving frontal and ethmoidal sinuses. External frontal sinus drainage (Howarth) operation:—On 7th December 1942 this man was admitted to hospital (neuro-surgical unit) suffering from a lacerated wound of the supero-medial aspect of the left orbit. X-ray showed comminuted fracture of the supero-nasal angle of the left orbital margin, involving the left frontal sinus, with scattered bone fragments in the medial part of the orbit. Both maxillary antra and the left ethmoidal sinuses were opaque. The case was referred to the ophthalmologist, who cleaned up and sutured the wound which healed by first intention and he was discharged from hospital two weeks later.

On 4th January 1943 (four weeks after injury) he reported with left frontal headache, diplopia (left superior oblique), tenderness and swelling in the region of the scar and slight purulent discharge from two small sinuses in the scar, through which bare bone could be felt with a probe. He was referred to the E.N.T. specialist and polypi were found in the left side of the nose. X-ray appearances were unaltered. Operation was delayed till 20th January, on account of a supervening acute rhinitis. During this interval there was little change in the local condition. At operation through a curved orbital incision as described in Case 1, a number of fragments of the orbito-frontal wall were found to have been driven into the frontal sinus and bone fragments had also been driven into the ethmoidal sinuses. Both frontal and ethmoidal sinuses contained pus. The latter also contained polypi but the frontal sinus mucosa looked reasonably healthy. The entire floor of the frontal sinus and a large part of the lateral wall of the ethmoid (lamina papyracea) were removed. (The anterior bony wall of the frontal sinus was *not* interfered with, thus avoiding disfigurement; nor was the frontal mucous membrane, with the exception of the portion covering the bony floor). The ethmoidal sinuses were completely exenterated. Pus was found in the sphenoidal sinus, the ostium of which was consequently enlarged. An adequate fronto-nasal duct was established by removal of a considerable portion of the frontal process of the maxilla and part of the nasal process of the frontal bone, particular attention being paid to the bony projection from the frontal bone. The anterior

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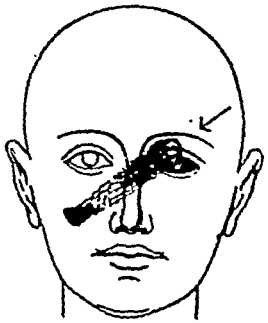
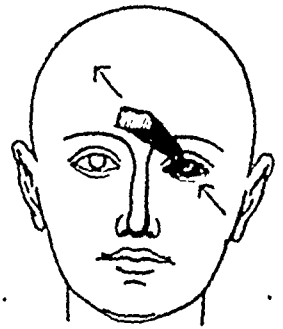


Case 1.



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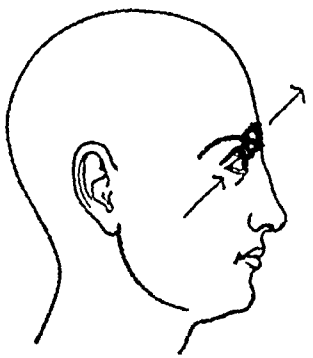

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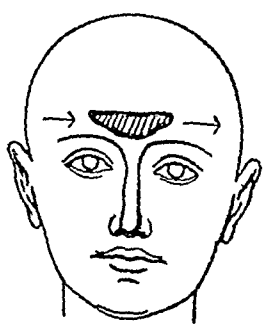

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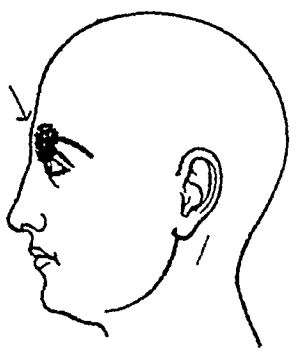

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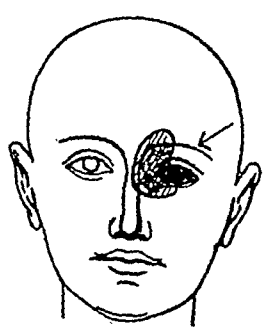

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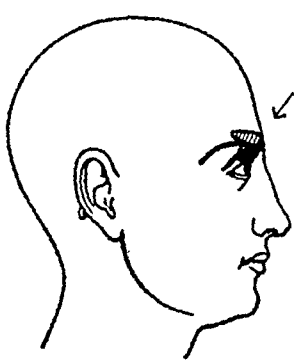

Case 8.

end of the middle turbinate was removed through the nose. A large nasal rubber drainage tube was inserted, with its upper end lying in the anterior part of the sinus. The wound was sutured with a small drain at the lower medial extremity. Exploratory puncture revealed pus in both maxillary antra which were drained intranasally. The wound was completely healed in twelve days. On discharge from hospital three and a half weeks after operation, the superior oblique diplopia was still present. He was instructed to report in four weeks, but has not been contacted since discharge.

CASE 3. Sgt. A. Aged 30. Shell wound of head, involving the left orbit and both frontal sinuses. Bilateral frontal sinus obliteration operation:— On 21st November 1941 this N.C.O. was hit by a piece of shell which entered the left orbit and passed obliquely through the frontal region. Removal of the left eye and debridement of the left frontal wound was carried out twelve to eighteen hours later, and he was ultimately evacuated to the base. His progress was stated to have been uneventful and he was referred to a maxillo-facial unit for plastic treatment. On 1st April 1942 (four and a half months after being wounded), before any plastic treatment had been commenced, he had a "fit" and was transferred to a neurosurgical unit, where he was found to have a persistent discharging sinus in the frontal region which communicated with the frontal sinus. The nose was healthy. C.N.S. findings were normal. X-ray showed comminuted fracture of the frontal bone involving both frontal sinuses, and opacity of the left maxillary antrum. Encephalography showed slight enlargement of the left anterior horn. The cisternal fluid contained 24 lymphocytes per c.mm. and total protein was 40 mgms. per cent. He was transferred to the E.N.T. Department two weeks later. On 23rd April (five months after being wounded) operation was carried out. At preliminary lumbar puncture the C.S.F. was found to contain less than 2 cells per c.mm. Exploratory puncture and lavage of the left maxillary antrum gave a clear return.

A curved orbital incision, as described in Case 1, was made on either side, and these were joined together across the bridge of the nose (anterior cross-bow). A second incision enlarged the oblique open wound over the frontal region, which was excised. The bone defect in the frontal region was found to communicate with both frontal sinuses and these communicated freely with one another, forming one large cavity filled with pus, polypoid tissue and some loose bone fragments. Most of the floor of the left sinus (*i.e.* roof of orbit) had been destroyed, also part of the posterior sinus wall, leaving a central area of exposed and badly-scarred dura about the size of half a crown. The operative procedure was essentially the same as described in Case 2, but both frontal sinuses were completely obliterated by the additional procedure of complete removal of what remained of the anterior bony walls and the entire mucous membrane. A nasal drainage tube was inserted on both sides and the wound was sutured without external drainage. A small area subsequently broke down, but it was completely healed in four weeks. On 10th June (seven weeks after operation), encephalography showed no change and the cisternal fluid contained 4 lymphocytes per c.mm. and 30 mgms. per cent. total protein. He was invalided a few weeks later. In April 1943 he was reported to be suffering from post-traumatic epilepsy. The fits had been controlled with luminal and he was now able to play tennis and was about to undergo plastic treatment.

DIAGNOSIS

X-ray examination formed an essential part of investigation in every case. Stereoscopic pictures proved helpful in some cases. Instillation of *lipiodol* through fistulæ leading into the frontal sinus and X-ray demonstration of its passage through the fronto-nasal duct were found to be of considerable prognostic assistance in Cases 8 and 9, both of which were regarded as border-line cases. This investigation led to the postponement of more radical operative treatment, with ultimate recovery.

TREATMENT

Sulphonamide.—In most cases one of the sulphonamides (preferably sulphadiazine) was commenced twenty-four hours before operation and was continued for four to five days thereafter. To tide the patient over the immediate post-operative period till administration by mouth could be resumed, it was given intravenously in those cases in which the dura had been involved, either by repeated injection or in a continuous saline drip.

Blood Transfusion.—Pre-operative hæmoglobin estimation and grouping were carried out, and in the more severe cases an intravenous drip was started at the beginning of the operation.

Anæsthesia.—Endotracheal nitrous oxide, oxygen and ether or continuous pentothal were the anæsthetics employed, after a preliminary injection of morphia and hyoscine. Whichever anæsthetic was given, an endotracheal tube was passed and the pharynx was packed. As it is frequently necessary to have access to both sides of the nose, the tube should invariably be passed through the mouth in these cases.

Operative Technique.—Nasal hæmostasis is facilitated by packing with ribbon gauze wrung out of equal parts of cocaine 10 per cent. and adrenalin 1 : 1000 at the beginning of the operation. The routine incision has been described in Case 1. Its extent laterally is largely determined by the lateral extent of the frontal sinus as seen on X-ray. Modifications in terms of pre-existing wounds and scars were of course necessary in a number of cases. Unless the incision was to be bilateral the eyebrow was not shaved. When available, diathermy is recommended for dealing with the numerous bleeding points. Removal of a large part of the frontal process of the maxilla and part of the nasal process of the frontal bone is essential for the establishment and maintenance of an adequate fronto-nasal duct, as in Case 2. It is considered that this procedure is of much greater importance than the introduction of a skin graft in this type of case. In obliterating the frontal sinus, removal of all mucous membrane and all overhanging bony margins must be absolutely complete so that the scalp and orbital tissues can come to lie in complete apposition with the inner sinus wall. In order to afford better drainage it is advisable to remove at least the anterior end of the middle turbinate and this should be done through the nose. It is most necessary that any other paranasal sinus which

TABLE II

Maxillary and Maxillo-Ethmoidal Sinus Cases

Case.	Nature of Injury.	Clinical Features.	Nature of Sinus Operation.	Interval between Injury and Operation.	Operation Findings.	Result.	Remarks.
10. Pte. G.	Gunshot wound of left orbit and maxilla, with loss of left eye	Persistent discharge from orbit	Left Caldwell-Luc	6 weeks	Bone fragments, polypi	Orbital discharge ceased within a few days	...
11. Pte. T.	Shell wound of left orbit, ethmoid and maxilla, with loss of left eye	Persistent discharge from orbit	Left Caldwell-Luc and trans-antral ethmoidectomy	5 weeks	Bone fragments, pus	Orbital discharge ceased within a few days	...
12. Sgt. W.	Shell wound of left side of external nose, involving right antrum	Nasal discharge and recurrent pain and swelling of medial aspect of right orbit	Right Caldwell-Luc and trans-antral ethmoidectomy	4 weeks	Bone fragments, pus	No recurrence	...
13. P.O.W. K.	Shell wound of left malar and maxilla	Persistent discharge from fistula in malar region	Left Caldwell-Luc and correction of malar deformity	7½ weeks	Bone fragments, adhesions ++	Malar sinus healed within a few days	...
14. Pte. R.	Shell wound of face, involving right antrum	Persistent discharge from facial fistula	Right Caldwell-Luc	3½ weeks	Metallic F.B., polypi	Face wound healed within a few days	Pre-existing antral infection probable
15. Capt. W.	Shell wound of face, involving right antrum	Persistent discharge from antrum through large face wound	Right Caldwell-Luc	2 weeks	Bone fragments, pus	Uninterrupted healing of face wound	...
16. Pte. T.	Shell wound of left orbit and maxilla, with loss of left eye	Persistent discharge from orbit. (Meningitis with recovery on sulphadiazine)	Left Caldwell-Luc	4 weeks	Bony roof shattered, metallic F.B., polypi, pus	Orbital discharge ceased within a few days	Pre-existing antral infection probable
17. Rfm. W.	Shell wound of right orbit and maxilla, with loss of right eye	Persistent discharge from orbit	Right Caldwell-Luc	5 weeks	Bony roof shattered, polypi, pus	Orbital discharge ceased within a few days	...
18. Gnr. T.	Bomb wound of right side of face, involving right antrum and left orbit	Face wound healed, but X-ray showed multiple bone fragments in antrum	Right Caldwell-Luc	6 weeks	Bone fragments, adhesions, mucosa thickened	Satisfactory	...
19. Pte. M.	Multiple penetrating shell wounds of (1) head, left parietal region; (2) left malar, maxilla and orbit, with loss of left eye	Malar wound broken down. (Wounds had been excised and closed at forward neurosurgical unit.) X-ray showed comminution of left malar and maxilla and a metallic F.B. in left posterior ethmoidal region	Left Caldwell-Luc and trans-antral ethmoidectomy	6 weeks	Bony roof and antero-lateral wall shattered, polypi, metallic F.B. 1½ × ½ × ½ in., high up in posterior ethmoid	Died of brain abscess, associated with parietal wound	Drainage of brain abscess carried out subsequent to sinus operation. At P.M.—Fracture of anterior fossa (roof of ethmoid) was found, with underlying dura intact
20. L/Cpl. McC.	Knocked off a lorry. Fracture of left malar and maxilla	Acute maxillary sinusitis. Intranasal antrostomy (in another hospital). Recurrent pain and swelling, necessitating incision and drainage of abscess in soft tissues and removal of sequestra	Left Caldwell-Luc and trans-antral ethmoidectomy	4 months	Bone fragments in antrum. Pus and polypi in antrum and ethmoid	Invalided to U.K. while still convalescent	No follow-up report received

After-Treatment.—A prophylactic course of one of the sulphonamides was only given in those cases in which the ethmoid had been explored. The antrum should be washed out daily from the second or third day, till the return is clear, by means of a naso-antral cannula.

SUMMARY

1. Twenty cases of wounds or injuries involving the paranasal air sinuses are recorded.

2. In 9 of these the frontal or fronto-ethmoidal region was involved, while involvement of the maxillary or maxillo-ethmoidal region occurred in 11.

3. The late operative procedures are described and technical points are discussed.

My thanks are due to Major-General J. C. A. Dowse, *C.B.E.*, *M.C.*, Director of Medical Services, M.E.F., for permission to publish this paper. To Lt.-Col. P. B. Ashcroft, *M.B.E.*, Major D. McKenzie and Captain G. B. Northcroft, *M.B.E.*, neuro-surgeons; Major J. E. Caughey, neurologist; Major W. H. Milligan, radiologist; Major H. B. Stallard, *M.B.E.*, Ophthalmologist; and Major M. C. Oldfield, *M.B.E.*, maxillo-facial surgeon; my thanks are also due for their collaboration in the care of these patients; also to Captain W. S. Lewis, neuro-surgeon, for his helpful interest. I am indebted to Major R. Gowans, otologist, for the details of Case 9.

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THE STANDARDISATION OF LIVER EXTRACTS FOR INTRAMUSCULAR INJECTION

By H. W. FULLERTON, M.D., M.R.C.P.

From the Department of Medicine, University of Aberdeen

THOSE who have the opportunity of seeing many cases of pernicious anæmia realise that, in general, the results of treatment cannot be regarded as satisfactory. It is true that, if complications affecting the nervous system have not occurred, no patient need suffer from any of the symptoms of the disease so long as adequate maintenance treatment is continued; but it is nevertheless a regrettable fact that this ideal is often not attained. One of the main reasons for this is that liver extracts for parenteral administration vary greatly in potency, and, in this country, there is no satisfactory way of indicating to doctors, first, that a particular extract is potent, and, second, how potent it is. The only method whereby the activity of liver extracts may be tested is by assessing their effect in cases of Addisonian pernicious anæmia in relapse. Accordingly manufacturers of extracts have enlisted the help of clinicians who are prepared to carry out the appropriate tests. But clinical testing is not obligatory and, from time to time, extracts have been issued which had little or no potency. The following case summaries illustrate this point:—

(1) Mrs J. had been receiving 4 c.c. extract A every ten days for several months. In spite of this her condition deteriorated, and on 9.10.41 Hb. was 48 per cent. and R.B.C. 1·78 mill. per c.m. Weekly injections of 4 c.c. extract B were then given, and on 11.11.41 Hb. was 86 per cent. and R.B.C. 4·10.

(2) Mr A. M. had received 4 c.c. extract A every four weeks as maintenance treatment. On 6.2.43 Hb. was 48 per cent. and R.B.C. 1·63. A single injection of 2 c.c. extract B was given, and in ten days Hb. had risen to 58 per cent. and R.B.C. 2·31.

(3) Mrs J. S. was given 2 c.c. extract A every two weeks as maintenance treatment for two years. On 1.3.43 Hb. was 60 per cent., R.B.C. 2·18. Fourteen days after a single injection of 2 c.c. extract B, Hb. was 72 per cent. and R.B.C. 2·98.

(4) Mrs D. became increasingly weak in spite of 2 c.c. extract A weekly for six weeks, and at the end of this time Hb. was 46 per cent., R.B.C. 1·73. Three c.c. extract B were injected and a week later 2 c.c. Fourteen days after the first of these injections Hb. was 72 per cent., R.B.C. 3·41.

To demonstrate even more clearly the very low potency of extract A, which is claimed by the manufacturers to be a concentrated extract, 5 c.c. were injected in a patient with an initial count of Hb. 36 per cent., R.B.C. 1·13. There was a slight increase in reticulocytes of doubtful significance (maximum, 5 per cent. on the fourth day) and fourteen days after the injection Hb. was 32 per cent., R.B.C. 1·23. A satisfactory response was then induced by small doses of another extract.

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These are some examples, seen recently, of relapses due to the use of extracts of little or no potency. When it is realised, first that the development of subacute combined degeneration of the spinal cord is a constant danger in these circumstances, and second, that if severe relapses have been fairly common, then at least some deaths probably resulted, it is clear that strenuous efforts should be made to prevent such occurrences. Experiences of this kind can be avoided only if extracts are tested by competent hæmatologists and if manufacturers do not issue extracts which have not been proved to be potent. There can surely be no doubt that these requirements should be made compulsory and that the results of the tests should be submitted to an impartial body for approval before extracts are issued.

The further question which arises is whether it is advisable to introduce some official method of assessing the potency of extracts in a quantitative manner. If this were practicable the treatment of pernicious anæmia would be greatly simplified. In the United States extracts must be clinically tested before being approved by an Advisory Board and, in addition, the Board assesses the potency of each extract in terms of "units." A "unit" is that amount of an extract which, when injected daily, produced a "satisfactory" reticulocyte response and rate of red cell increase in at least three cases of pernicious anæmia. Figures showing the responses which may be regarded as "satisfactory" are issued by the Board. Thus if $\frac{1}{2}$ c.c. of an extract injected daily gives satisfactory responses, that extract contains 5 units per c.c. Some of the American extracts have the highest rating awarded by the Board, namely, 15 units per c.c. In Canada a somewhat similar method has been introduced, the main difference being that the injection may be made at weekly intervals and a unit is therefore the volume of the weekly injection necessary for a satisfactory response divided by 7. It is clear that in this country the question of adopting some method of standardisation is receiving much attention and, therefore, the following account of observations on different methods of assay may be of interest.

I. Effect of a Single Dose

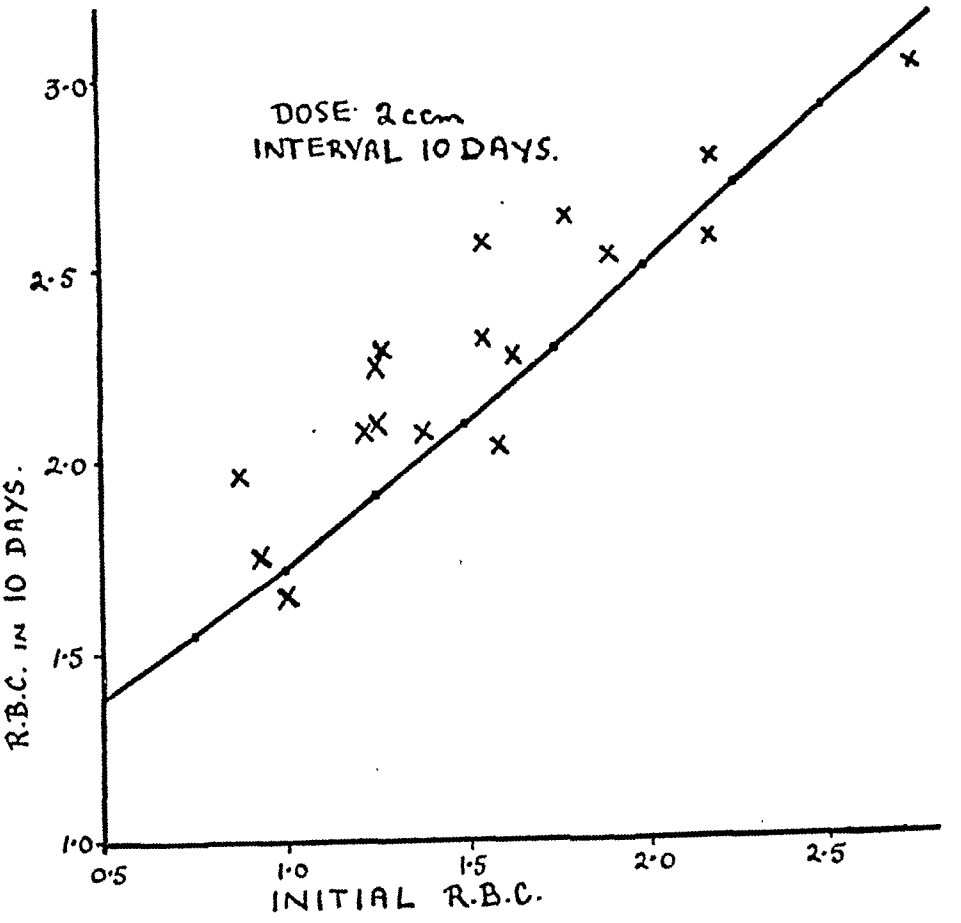
Probably the most common method of assessing the potency of liver extracts in this country is to estimate the reticulocyte response and rate of red cell increase during a fixed period after a single injection. This method depends on the fact that the rate of blood regeneration cannot be increased beyond a certain extent, however great the dose. Accordingly the object is to find the lowest dose which stimulates optimal regeneration during the period of observation. Various criteria for satisfactory reticulocyte responses and rates of red cell increase have been proposed which do not differ greatly from each other. In the following account the figures provided by the U.S.P. Advisory Board have been used to calculate the responses to treatment which may be regarded as satisfactory.

During the past few years various batches of one brand of liver extract (referred to in the text as extract B) have been tested for potency in this way. All the patients had uncomplicated pernicious anæmia and an adequate control period was observed before treatment. It is convenient to consider separately the rates of red cell increase and the reticulocyte responses.

TABLE I

Dose 2 c.c. Period of Observation 10 Days

Initial R.B.C. count	0·88	0·93	1·0	1·22	1·25	1·25	1·27	1·39	1·55	1·55	1·59	1·63	1·78	1·90	2·18	2·18	2·75
Final count	1·97	1·76	1·65	2·08	2·10	2·25	2·29	2·08	2·58	2·32	2·05	2·28	2·65	2·55	2·81	2·60	3·06
Expected count	1·6	1·6	1·7	1·9	1·9	1·9	1·9	2·0	2·1	2·1	2·2	2·2	2·3	2·4	2·6	2·6	3·1



(*a*) *Rate of Red Cell Increase.*—In 17 cases a single injection of 2 c.c. extract B was given and the red cell count was determined at the end of ten days. The initial red cell counts varied from 0·88 to 2·75 mill. per c.c. From the chart issued by the U.S.P. Advisory Board the expected red cell count at the end of the period of observa-

tion was noted in each case. The results are presented in Table I and the Chart. In this chart the responses to treatment are plotted as single points with the abscissa representing the initial red cell count and the ordinate representing the count at the end of the period of observation. The line in the chart was drawn through points plotted in this way taking the expected count at the end of the period of observation from the data provided by the U.S.P. Advisory Board. Thus any point lying above this line represents a satisfactory response; any points lying significantly below it indicate that the response is unsatisfactory.

One objection sometimes put forward against any method of assessing the potency of liver extracts quantitatively is that the responses of patients are so variable that any such method is bound to be grossly inaccurate. This contention is hardly borne out by the figures in Table I and Chart. Indeed when one considers the margin of error of red cell counting (estimated as ±16 per cent. by Berkson, Magath and Hurn, 1940) and the fact that the different batches (11 in number) of extract B may have varied somewhat in potency, the close correspondence between the actual and the expected red cell counts is quite striking. The figures show clearly that 2 c.c. extract B produced satisfactory red cell regeneration during the ten days following injection.

TABLE II

Dose 2 c.c. Period of Observation 20 Days

Initial R.B.C. count .	1·27	1·39	1·59	2·18	2·18	2·75
Final count . . .	2·86	2·50	2·65	2·90	3·10	3·09
Expected count . .	2·9	3·0	3·1	3·4	3·4	3·7

TABLE III

Dose 3 c.c. Period of Observation 10 Days

Initial R.B.C. count . .	1·0	1·45	1·62	1·65	1·98	2·25	2·30
Final count	2·1	1·95	2·72	2·15	2·90	2·76	3·10
Expected count . . .	1·7	2·0	2·2	2·2	2·5	2·7	2·8

TABLE IV

Dose 3 c.c. Period of Observation 20 Days

Initial R.B.C. count . . .	1·45	1·62	1·98	2·25
Final count	2·88	3·01	3·40	3·60
Expected count . . .	3·0	3·2	3·3	3·4

The results when the dose and the period of observation were varied are presented in Tables II, III and IV. It is clear that, while

a dose of 3 c.c. maintained a satisfactory rate of response when the periods of observation were ten days and twenty days, the response to 2 c.c. was not maintained at a satisfactory rate during the second half of a twenty-day period in five of six cases. Therefore this " single dose " method of assay was accurate enough to differentiate clearly the effects of 2 c.c. and 3 c.c. when the period of observation was twenty days.

(*b*) *Reticulocyte Response.*—It is not proposed to discuss in detail the reticulocyte responses of the cases presented in Tables I, II, III and IV because, in some, an estimation was not made on each day of the period of observation. While it is true that a reticulocytosis occurred in every case, the magnitude of this response varied considerably. For the 14 cases in which a daily count was made, the maximal figure, which occurred on the fourth, fifth or sixth day after injection, was expressed as a percentage of the expected figure calculated from the data provided by the U.S.P. Board. These percentages ranged from 40 to 218. Accordingly, although a reticulocytosis is the first definite indication of response to treatment, its magnitude is considered to be a less reliable indication of optimal dosage than the red cell count. This opinion is shared by others (Della Vida and Dyke, 1942).

II. Method of the U.S. Pharmacopœia Advisory Board

This method, as indicated previously, involves the administration of small daily doses for a period of at least two and preferably three weeks; thereafter injections of seven times the daily dose may be given at weekly intervals. The daily dose which is considered by the Board to have produced satisfactory responses in 3 cases represents one " unit " of activity. It has been suggested that an equivalent " unit " may be calculated from the response produced by a single dose by dividing the number of days during which a satisfactory response is observed by the number of cubic centimetres injected. For example, the figures in Table I indicate that 2 c.c. extract B produced a satisfactory response for at least ten days; hence extract B contains not less than $\frac{10}{2} = 5$ " units " per c.c. For convenience units determined in this way are referred to hereafter as " single dose units " to distinguish them from U.S.P. units. Emery and Hurran (1945), who adopted fourteen days as the period of observation, believe that a " single dose unit " is approximately equal to a U.S.P. unit. However, it seems unlikely that this is the case. After an injection of liver extract several days elapse before any effect on the blood count is observed, and regeneration then continues for a variable time depending on the dose. Therefore, if a single injection of 1 c.c. produces a satisfactory response during the subsequent fourteen days, it does not follow that $\frac{1}{14}$ c.c. daily of the same extract will give a similar response *in that time*. In the first case all the anti-anæmic factor

in 1 c.c. (excluding an unknown and probably very small proportion which is not utilised) has had fourteen days in which to exert its effect; in the second case only $\frac{1}{14}$ c.c., that is, the first daily injection, has had a similar time in which to act, and it is probable that the doses given in the last few days of the period of observation will have had no effect on the blood count at the fourteenth day. Moreover, it is clear that when daily doses are given the peak of the reticulocyte response will occur before the injections given during the latter part (approximately one week) of a fourteen-day period and, therefore, will not be influenced by them. Accordingly it is unlikely on theoretical grounds that one U.S.P. unit is approximately equal to one "single dose unit."

The difference between the two units is illustrated by the following results. Table I shows that extract B contains at least five "single dose units" per c.c.; Tables II and IV indicate that it contains not more than ten and not less than seven "single dose units" per c.c., since 3 c.c. gave satisfactory responses over twenty days and 2 c.c. did not. Six cases were given 0·2 c.c. daily for ten days, and in 4 of them this was continued for twenty days; one case received 0·25 c.c. daily for twenty days and another for ten days. The results, which are presented in Table V, compare unfavourably with the

TABLE V

Small Daily Doses

	0·2 c.c. Daily.										0·25 c.c. Daily.		
	Period: 10 Days.						Period: 20 Days.				10 Days.		20 Days.
Initial R.B.C. count	0·82	1·27	1·53	1·55	1·72	2·56	0·82	1·55	1·72	2·56	1·49	1·52	1·52
Final count	1·63	1·50	2·10	1·55	2·50	3·09	2·48	2·73	3·0	4·05	1·94	2·22	2·60
Expected count	1·63	1·90	2·15	2·12	2·3	3·0	2·6	3·1	3·2	3·6	2·1	2·1	3·1

responses produced by 2 c.c. over ten days and 3 c.c. over twenty-days. It may be deduced that extract B contains less than 5 U.S.P. units per c.c. (since 0·2 c.c. daily gave responses which cannot be regarded as entirely satisfactory), and, therefore, as would be expected on theoretical grounds, 1 U.S.P. unit represents considerably more activity than one "single dose unit."

Discussion

The main purpose of this paper is two-fold; first, to demonstrate that some official method of control is strongly indicated so that the issue of inactive extracts may be prevented; and second, to show that it is practicable to adopt a method of measuring potency in a

quantitative manner. A secondary object has been to give examples of different methods of assay and to point out that " units " of potency determined by these methods cannot be regarded as equal. It is not suggested that enough data have been presented to make possible a clear choice of the best method of assay; unfortunately the number of suitable cases has been insufficient for this purpose. But from the data which are available the " single dose method " seems to have some advantages over the U.S.P. method. One of these is its simplicity and another is the fact that more uniform results are obtained by its use than with the U.S.P. method. In 2 of the 6 cases treated with 0·2 c.c. daily the response was delayed; the reticulocyte peaks occurred on the eight and tenth days as compared with the fifth and sixth days in the cases given an initial injection of 2 or 3 c.c. and the start of the red cell increase was correspondingly later. In both of these cases the rate of red cell increase was satisfactory after it had started, but the long latent period naturally resulted in an unsatisfactory count at the tenth day. It must be borne in mind, however, that 0·2 c.c. extract B is apparently less than one U.S.P. unit; the delays referred to might not have occurred if larger daily doses equivalent to 1 U.S.P. unit had been given.

One disadvantage of adopting a measure of potency different from the U.S.P. unit is the confusion which would result. In Canada the method adopted allows the dose to be given weekly. It will be realised therefore that the " single dose method " would introduce a third measure of potency, and " units " determined by each of these methods would represent different degrees of activity. It is to be hoped, however, that the issue will not be obscured by considerations of this kind. Further work is necessary to determine more precisely the differences between the various units. The important point is that while the accuracy of any of the methods is not great, the adoption of any one would be a great step forward.

It should be pointed out that although a ten-day period of observation was chosen in most of the cases referred to above, it is not thought that this is the most suitable one. Part of this work was done when it was considered sufficient to decide only whether an extract was or was not potent. For quantitative assay a longer period is desirable, and I would suggest twenty days with a determination of the red cell count every fourth day. In this way the response would be represented by a series of five red cell counts which could be plotted as a curve and compared with that representing the expected rate of red cell increase. This would reduce the effect of the experimental error inseparable from red cell counting. During the period of observation a reticulocyte count should be done daily until the peak is clearly passed. The occurrence of a reticulocytosis at the expected time is early and valuable evidence that the extract is potent, but a close approximation to the expected figure need not be demanded. Using this method the potency of an extract could be determined by

finding the lowest volume which produces a satisfactory rate of red cell increase during the twenty days after injection in 3 cases of uncomplicated pernicious anæmia in relapse. The potency could then be expressed in "units" by dividing 20 by the number of cubic centimetres in the injection. The results presented above suggest that this method would be sufficiently accurate. The effects of 3 c.c. extract B for twenty days are clearly of a different order from those produced by 2 c.c., and therefore the extract can be said to contain between 7 and 10 "single dose units" per c.c. A small series of cases given 2·5 c.c. and followed for twenty days might have enabled the degree of potency to be determined within still narrower limits.

Carr (1945) has objected to the use of the term "unit" in this way on the ground that it is inappropriate "except where an exact determination of potency can be made in comparison with that of a standard stable substance which has been rendered available for this purpose." This contention may have some justification but it is difficult to suggest an alternative term. Carr believes that an assessment of potency on a numerical basis is not justified, and recommends that an extract should be considered to possess "full activity" if "a given number of cubic centimetres" has produced a satisfactory increase in the red cells in ten or fourteen days in 3 cases of pernicious anæmia. But it is obvious that manufacturers of a concentrated extract are entitled to claim that a small dose of their product produces this satisfactory response and to state in cubic centimetres the size of that dose. There is, therefore, no essential difference between such a method of assay and the "single dose method" discussed above. Assessment on a numerical basis becomes unavoidable whether or not the potency is expressed in terms of "units."

SUMMARY

1. Clinical testing of liver extracts before issue should be made compulsory.

2. Assessment of potency on a quantitative basis is practicable.

3. "Units" of potency determined by the different methods of assay commonly used are not equal.

I wish to express my thanks to Professor R. S. Aitken, Dr A. Greig Anderson, Dr A. W. Hendry and Dr John Smith, and many general practitioners, for their help and co-operation in this work.

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BLOOD CULTURE: METHODS AND RESULTS

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THE following paper discusses the technique employed, and the results obtained, in a series of 120 routine blood cultures performed in the Royal Infirmary of Edinburgh between 17th April and 26th December 1944.

Certain modifications in technique were introduced in April 1944 as it was felt that the existing methods were unsatisfactory, chiefly owing to the high percentage of contaminated cultures. In one period nearly half the specimens received were found to be contaminated. The blood was taken with Record syringes, which were boiled up and fitted together in the wards, and it was felt that it was during this process that the contaminants were introduced. The media used were usually ordinary and trypsin broth, and bile salt in suspected enteric fever.

The changes in technique adopted were as follows :—

(1) Sterile syringes were issued to the wards along with the culture medium. These were all-glass 10 c.c. syringes, with a flange at the top end of the barrel. The syringe, with needle in position, was placed in a test-tube, the flange fitting over the rim of the tube. The handle of the piston and the flange, which remained outside the test-tube, were protected by a paper covering tied in place with string. The whole was sterilised by autoclaving. For use it was necessary only to unloose the string, remove the paper cover and take the syringe out of the test-tube.

(2) Along with the syringe there were sent a flask containing 100 c.c. ordinary broth, and a sterile screw-capped bottle containing 1 c.c. sterile 3·8 per cent. sodium citrate solution. Five cubic centimetres of blood were to be added to the flask of broth and 5 c.c. to the citrate solution, rotating the latter thoroughly to prevent coagulation.

In the laboratory the citrated blood was cultured as follows: two tubes of agar were melted in a water-bath and cooled to 42° C. Then measured quantities of the blood (usually 1 c.c. and 3 c.c.) were added to each with a sterile pipette; the contents of each tube were poured into a sterile Petri dish, mixed thoroughly, allowed to harden, and incubated. These are described as " plate cultures." One cubic centimetre of the citrated blood was inoculated into a tube of Robertson's meat medium for anaerobic culture. These methods of culturing citrated blood are similar to those advocated by Kolmer and Boerner.

The citrated blood could also be used for inoculating other media in special cases, *e.g.* bile salt in suspected typhoid. Since the cultures

from citrated blood must be set up shortly after the blood is obtained, this method was impracticable in the case of blood cultures taken at night. In these cases usually two flasks of broth were inoculated with about 5 c.c. of blood each. (In such cases, if one flask was contaminated and the other not, the case was counted as one-half in reckoning the total number of contaminated specimens.)

Other special procedures adopted were: incubation in an atmosphere of 10 per cent. CO_2 in suspected cases of abortus or gonococcal infection; addition of penicillinase to the media in cases receiving penicillin treatment.

Various methods of cleansing the patient's skin have been advocated; thorough cleansing with hot water and soap, followed by the application of spirit and tincture of iodine, appears to give satisfactory results.

"Surgical cleanliness of the hands is not necessary, but in order to guard against contamination from the skin it is essential that the person taking the blood should not have wet hands. The syringe and the patient's skin should be kept dry. It is advisable to remove the needle from the syringe before adding the blood to the various media. . . . It is probably an advantage, and in the case of gonococcal infection a necessity, to warm the media to 37° C. before the addition of the blood" (Butler). It is also advised that the mouths of the flask and bottle should be flamed at the time of opening.

Subcultures from the broth cultures were usually made after 48 hours' incubation, but earlier in cases of special urgency, and were repeated if the first was negative. In all but three cases, however, the culture either showed organisms within 48 hours, or remained negative. The culture was kept for at least 10 days, and in some cases up to three weeks, if no growth appeared. The plate cultures were examined after 24, 48, and 72 hours' incubation, and if colonies appeared subcultures were made to identify them. The anaerobic culture was examined at similar intervals and subcultures made aerobically and anaerobically as appeared necessary.

The Problem of Contamination

The following organisms were invariably regarded as contaminants: *Staphylococcus albus* (coagulase-negative), diphtheroids, and subtiloid bacilli. Such organisms were obtained from the broth culture in 16½ out of 120 cases (13·8 per cent.) in the present series.

In a series of 160 routine blood cultures sent to this laboratory during the same months of 1943, the broth culture was contaminated in 79 cases (49·2 per cent.).

The proportion of contaminated cultures has thus been reduced to little more than one-quarter of the former figure, but it is still regrettably high, and could probably be further reduced considerably by a more strict attention to aseptic technique, as described above.

The proportion of contaminated specimens varied considerably according to the time of day at which the cultures were taken :—

Time of Taking.	No. of Cultures.	Contaminated.	Per Cent.
6 a.m. to 11.59 a.m.	21	2	9·5
12 noon to 5.59 p.m.	39	4½	11·5
6 p.m. to 11.59 p.m.	31	7	22·6
12 midnight to 5.59 a.m.	10	2	20·0

In the remaining 19 cases the hour of taking the culture was not stated. The higher incidence of contamination in the evening and at night may perhaps be attributed to poor lighting in the wards, and fatigue on the part of doctors and nurses.

Apart from those regarded invariably as contaminants, the following were the organisms obtained: *Streptococcus viridans*, 15 cases; *Staphylococcus aureus*, 9 cases; anaerobic streptococci, aerobic non-hæmolytic streptococci, *B. proteus*, each 2 cases; *Staphylococcus pyogenes albus*, *Streptococcus hæmolyticus*, *Pneumococcus*, *Streptococcus fæcalis*, *B. coli*, atypical *B. coli*, each 1 case.

Also coagulase-positive staphylococci were found in two cases on anaerobic culture only, and were not regarded as significant.

The final diagnosis was ascertained in all cases.

Negative Cultures

In many of the cases where the blood culture was negative the patient was ultimately found to be suffering from some condition in which a positive blood culture would have been unlikely, *e.g.* miliary tuberculosis, progressive muscular atrophy, amœbic abscess of liver, arsenical hepatitis. Several patients proved to have malignant disease.

There were three cases of undoubted staphylococcal septicæmia. These had all received treatment with penicillin in amounts of 270,000, 530,000 and 1,300,000 units respectively before the culture was taken.

Ten cultures were from patients suffering from subacute bacterial endocarditis. All had previously given positive cultures and had since been treated with penicillin or full doses of sulphonamide. No case of subacute bacterial endocarditis failed to give a positive culture prior to treatment.

There was one case of meningococcal meningitis. The patient had received 2 gms. sulphathiazole before the culture was taken.

Special measures of cultivation were employed, as noted above, in cases of suspected enteric, brucella and gonococcal infections, but the results were negative in all cases. This agreed with the clinical diagnosis.

VALUE OF THE DIFFERENT MEDIA

(1) *Plate Cultures* were set up in 75 of the 120 cases. Contaminating organisms were obtained from the plates in only 3 cases, while the broth cultures were contaminated in 6 cases.

In 11 cases organisms (other than contaminants) were obtained from both plates and broth cultures. In 5 cases the broth culture was positive and the plates negative, the organisms being *Staphylococcus aureus*, non-hæmolytic streptococcus, *Streptococcus fæcalis*, *B. coli* and atypical *B. coli*.

In 3 cases the plate was positive and the broth negative. In all cases the organism was *Streptococcus viridans*.

In one of these cases the finding was of doubtful significance; the patient had a *B. coli* urinary infection.

Of the other two specimens, one was from a patient with subacute bacterial endocarditis. Two previous broth cultures had been positive for streptococcus viridans. The third culture followed a course of 900,000 units of penicillin with 125 mgm. heparin. No organisms were obtained from the third broth culture, but there was a very scanty growth of streptococcus viridans in the solid medium (2 colonies from 3 c.c. blood). Subsequent cultures were negative in both broth and plates.

The remaining specimen was from a patient suffering from infected patent ductus, with blood culture positive for streptococcus viridans on two occasions. Just after ligation of the ductus a specimen of the blood was taken; broth culture was negative, but plate cultures showed a growth of streptococcus viridans 1 per c.c. Later cultures were negative in both media.

The solid medium thus appears to be superior to the broth culture for the isolation of streptococcus viridans when scanty, though inferior for some other organisms.

Elliot (*Journ. Path. and Bact.*, 1938) records two cases of subacute bacterial endocarditis in which attempts to grow the organisms in whole blood added to citrate broth failed. But streptococci were isolated from the whole blood samples during the first few hours of incubation by removing 1 c.c. quantities of the blood and plating in agar. He pointed out that leucocytes, especially polymorphs, remain actively phagocytic to streptococcus viridans for at least 24 hours after the blood has been added to a nutrient medium, and that the organisms commonly exhibit a "lag" phase of growth, during which period they are exposed to various inimical influences in the blood which are not completely abolished by dilution. Hence when whole blood is added to a nutrient broth the results may be unreliable, if the organisms are scanty.

The use of a solid medium enables an estimate of the number of bacteria present per c.c. of blood to be made. This may be of some diagnostic and prognostic value, *e.g.* in the cases of staphylococcal

septicæmia, one specimen showed a count of 116 per c.c.; the infection was fatal within a few hours. In staphylococcal septicæmia counts of over 50 per c.c. usually indicate a fatal outcome (MacNeal and Frisbee, 1932). Another staphylococcal case, which was fatal in five days, had a count of only 5 colonies per c.c. This was perhaps due to the fact that the patient had completed a course of 35 gms. sulphathiazole on the previous day. On the other hand, a case with a count of one colony per c.c. recovered under treatment.

In the cases of subacute bacterial endocarditis the colony count varied from 1 to 69 colonies per c.c.

A striking instance of the value of the colony count was afforded by the case of infected patent ductus, where the colony count fell from 31 per c.c. just before ligation to 1 per c.c. just after ligation of the ductus.

(2) *An anaerobic culture was set up in 73 of the cases. The medium* was found to be contaminated in six cases. In two others there was a growth of coagulase-positive staphylococci, but as such organisms were not obtained from the broth and plate cultures, and the patients showed no evidence of staphylococcal infection, these were regarded as probably laboratory contaminations. The broth culture was contaminated in 6 of these cases. The higher rate of contamination in the anaerobic medium might be due to the greater amount of manipulation in setting it up.

In 11 cases both aerobic and anaerobic cultures were positive, the same organism being obtained in each.

In one case different organisms were obtained from the two cultures. This was a case of empyema where staphylococcus aureus was obtained from the broth culture, diphtheroids and non-hæmolytic streptococci from the anaerobic culture. As the case record could not be found, it was unfortunately impossible to assess the significance of these results.

The broth culture was positive and the anaerobic negative in 5 cases. The organisms were *Streptococcus viridans*, *B. coli*, atypical *B. coli*, *Streptococcus fæcalis* and *Pneumococcus*.

The anaerobic culture was positive and the broth negative in two cases. The organisms were anaerobic streptococci.

The results with the anaerobic medium have been disappointing; this is probably due to the fact that very few cases of puerperal sepsis were included in the series.

Conclusions

(1) The adoption of a different technique of blood culture resulted in the reduction of the proportion of contaminated cultures from nearly one-half to less than one-seventh of the total. Precautions are suggested to lower this proportion still further.

(2) Staphylococcus aureus was isolated in all cases of staphylococcal

septicæmia except where penicillin treatment had been given, and the finding of this organism appeared to be significant in the great majority of cases. Streptococcus viridans was isolated in all cases of subacute bacterial endocarditis except after penicillin treatment and was significant in nearly all cases.

It is advised that cultures should not be taken during or just after treatment with penicillin or sulphonamides.

(3) The plate culture proved to be superior to the fluid medium for the isolation of streptococcus viridans, having the additional advantage that a colony count could be made.

(4) The anaerobic culture medium gave disappointing results, probably owing to the fact that there were few cases of puerperal infection in the series.

I should like to express my gratitude to my chief, Dr W. R. Logan, for his advice and encouragement; also to the clinicians of the Royal Infirmary for their help and co-operation, and in particular to Dr A. R. Gilchrist.

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DESPATCH OF MATERIAL FOR HISTOLOGICAL EXAMINATION

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THE following observations are deductions from the experience and practice of the Royal College of Physicians Laboratory, Edinburgh. During the year 1944 the Histology-Hæmatology Department issued 7152 written reports, an average of 22·85 per week-day. Of these reports 1866 were on tumours. The procedure can well be described as being on a mass scale. It is perhaps necessary to emphasise that these instructions refer mostly to the despatch of material and its treatment before its arrival in the pathologist's hands and not to the pathologist's own treatment of it. More importance attaches to biopsy tissue than to post-mortem specimens, if only because the material belongs in the one case to a living patient. Similar principles, however, apply in both cases. With the use of the word " despatch " it may be assumed that the specimen is to go to some distance and is not merely handed over to the pathologist on the spot A further assumption, not always applicable, is that it is to be sent by post and that the particular examination is to be carried out at a central laboratory. The necessity for centralisation is greatest, perhaps, in histological work on the grounds of experienced verdicts and of economy in time, labour and money. At least, that may be maintained for cancer diagnosis. Postal regulations are very strict as regards pathological material, must be read, and, in the main, are directed to prevent the leakage of fluids *en route*. If parcels are found leaking they are liable to be, and very often are, destroyed forthwith. Out of thousands of parcels sent to this laboratory, year after year, not more than half a dozen have failed to arrive for this reason.

Biopsy material for the pathologist may vary greatly in size and may be divided, on this simple basis, into (1) large, such as a breast and axillary glands; (2) medium, such as an encapsuled tumour; and (3) small, which may be exemplified by uterine curettings. These vary a little in their mode of despatch, but there is very little variation in the principles of treatment applied to the material. The injunctions are mainly three: (1) Place the material immediately in fixative without any previous washing in water. (2) Send it for examination without cutting into it. (3) Transmit it to the pathologist without delay. These requirements are general and not entirely rigid. Receptacles containing fixative or wrappings soaked in fixative should always be ready in the out-patient room and the operating theatre to receive material. A standard and admirable fixative is 10 per cent. formalin made up with tap-water. This penetrates well and allows

of transfer later to the feebly penetrating Zenker or Helly fluids, but should not be allowed to act for too long if a certain amount of shrinkage of tissue is to be avoided and the cytological appearances are to be well preserved. Formalin-fixed tissue, after washing, can be frozen and sections made to expedite diagnosis. If the diagnosis is doubtful a frozen section is not very satisfactory. A quick paraffin section, which, however, requires individual attention, can be obtained from formol fixed tissue in twenty hours. Our own practice for paraffin embedding is to transfer fresh tissue to 10 per cent. formalin, leave for twenty-four hours and then pass to Helly's fluid.* There is no advantage in passing formalin-fixed tissue after about seven days to Zenker or Helly's fluid. Such tissue suffices for section, but is no longer reactive. On the other hand, Helly or Zenker succeeding formalin fixation of not more than forty-eight hours will produce a very desirable further fixation with excellent cytological results, and the tissue is easy to cut. A report should be ready in five days after receipt of formalin-fixed tissue. Small tissue might be placed direct in Zenker's or Helly's fluid, but one disadvantage is that both of these colour the tissue uniformly yellow and distinctive macroscopic features become obliterated. A considerable volume of fixative by comparison with that of the tissue is always required.

Any glass receptacle, bottle, test-tube or specimen tube with sound fitting cork or screw top will serve for despatch, but bottles with a narrow neck should be avoided because the tissue will swell and is apt to be maltreated in removal. The fluid should come up to, or nearly up to the cork because there will be better cushioning and less likelihood of damage by shaking in the post. The cork should be well secured with plaster tape and the tube or bottle wrapped in wool or other packing material to prevent breakage. If the tissue cannot be sent off immediately it should, at least, be despatched as soon as possible. Some further particular advice applies to material according to its size.

1. *Large Material.*—The surgeon may wish to see the type of lesion he has been dealing with. In that case he should not gash the organ but adopt a routine procedure, which—again in general terms—may be to transect tumour, tissue, or organ in that axis which will include tumour, nipple, hilum, glands and adjacent tissue, if these are present, in the one plane sweep. This cut, or successive cuts, should not go clean through but should leave some tissue to act as hinge. In that way inspection is permitted and the whole can be closed up again. Too much manipulation of the organ is to be avoided. Pressing of a finger into a tumour to judge its consistence is a species of histological maltreatment. A whole organ and adjacent tissue may be too large to send immersed in fixative. In that case a portion can be sent and should be as large as is conveniently possible. On no account must either the organ itself or the selected portion of it be

* Mercury bichloride, 5; pot. bichromate, 2·5; sod. sulphate, 1; formalin, 5; distilled water, 100. The sod. sulphate may be omitted.

placed on dry gauze, since this has a most powerful desiccating capillary effect, nor indeed should any drying of material be allowed to take place. Desiccation of the specimen before embedding is a great handicap to the histologist and diagnostician. It is advisable to retain the remainder of the tissue until the histologist's report has been received, as a further specimen may be required for diagnosis, or the material may prove to be of such high scientific value that it should be distributed.

2. *Medium-sized Material.*—Economy and convenience may prevent the despatch of all the material and a portion has to be selected. The guiding principles here are that (1) it should have an external, probably convex, surface as well as a plane section surface; (2) it should not be a mere shaving but be, at least, $\frac{1}{4}$ to $\frac{1}{2}$ inch thick; (3) it should include directional tissue such as skin, mucosa, cortex and medulla, capsule, pelvis, hilum or root, duct, etc.; (4) it should contain the advancing margin, as well as a diagnostic field, of the lesion; (5) it should contain unaffected as well as simply affected tissue; (6) it should contain a note to indicate and some mark to show where it is desirable to obtain microscopic section.

If possible, despatch should be in fluid fixative, but if it is too large it may be wrapped in formalin-wet linen bandage or cloth and securely covered in waterproof gutta-percha tissue, or in the very convenient cellophane.

3. *Small Material.*—Still the injunction holds good, and even more emphatically, to pass this straight and unwashed to formalin fixative. On no account must it be placed on the disastrously desiccating, dry gauze of the operating room. As uterine curettings, endoscopic and canula biopsy material are both valuable and scanty, precaution should be taken not to lose any. It may be wrapped in a moistened close-textured linen bandage bag and tied with thread. Moistened gauze, although without drying effect, is not to be recommended, as small particles of tissue find their way into the meshes and may be lost.

Where not too large several pieces of tissue, even from different cases, may be sent in one bottle, but in that case each piece must be carefully threaded with an identification tag. It ought scarcely to require emphasis that full information regarding the case, as well as an identification tag, is obligatory under all circumstances if the report to be made is to repay the sender.

A central laboratory is usually prepared to send to regular clients forms, bottles with fixative, and a stained section, on the understanding that these are duly returned.

This account has referred to the despatch of histological material, but if bacteriological, serological, hæmatological or biochemical examinations were desirable it would be necessary to send unfixed material also.

It may be useful to set out in abbreviated and mandatory form the instructions for fixation and despatch of biopsy material and, perhaps,

it would be worth while having such instructions typed, framed and hung up for scrutiny.

Preparation of Histological Material for Despatch

(1) Take over the material [1] from the operator.

(2) Wrap it up temporarily in sterile cloth soaked in 10 per cent. formalin fixative [2] or, if small, pass straight into a specimen tube [3] filled [4] with formalin fixative and apply screw top or cork.

(3) Examine the large specimen gently and, if necessary, make one or more parallel transections in its long axis, the first plane of which should pass through lesion, skin or mucosa, nipple, hilum of organ, anatomical guide post, surrounding structure, etc., so as to give a clear view of anatomical relations.

(4) Reconstitute the specimen for despatch to the pathologist, wrapping it in 10 per cent. formalin soaked cloth or gauze, covering it with waterproof jaconet or cellophane and enclose the whole with its packing in a tin or box.

(5) If the specimen cannot be sent as a whole, remove one or more suitable portions to include advancing margin or capsule, diagnostic centre, unaffected tissue and adjacent structures useful for localisation and diagnosis, such as skin, bone, mucosa, extensions to lymph nodes, metastases, etc.

(6) Drop the selected portions, of not less than one quarter inch thickness [5] into specimen tube containing formalin fixative.

(7) Fasten the cork or screw top securely with adhesive tape to prevent leakage in the post.

(8) Pack the specimens along with sufficiently full and legible [6] notes which should include, at least, age, sex, married state, time of removal and tentative diagnosis; but these notes are greatly improved by further relative clinical detail.

(9) Despatch as soon as possible [7] to the pathological laboratory.

(10) Expect a report in five or six days [8] after receipt unless prolonged treatment such as decalcification is necessary.

(11) Add any special information required.

Notes

[1] It is better not to wash the specimen unless much covered with blood. If the material has been deposited on dry gauze, get it detached as quickly as possible and into fixative to prevent capillary-drainage desiccation by the gauze. Drying ruins the specimen especially when small.

[2] Composition: formalin 1; tap water 9.

[3] If the specimens are fragmentary it is advisable to tie them all up into a little bag of linen (not gauze) and place the whole thus protected from dispersal, in the fixative.

[4] Inclusion of any appreciable volume of air should be avoided, because it is apt with the fluid to cause injury to the material in transit.

[5] If the specimen is too thin it is difficult to embed and is apt to curl up.

[6] Block letters for the name of patient and for signature are advisable. The name of the chief is more important for laboratory record than that of the resident.

[7] It may be that, for reasons of economy, several pieces of material are retained in fixative for some days so as to be despatched in one parcel. Retention in formalin for too long causes undesirable shrinkage of the tissue.

[8] Frozen sections are quick but may not be reliable. A stained, thin, paraffin section of already fixed tissue can be put through for report in twenty hours, but should only be asked for in case of special urgency, since it requires individual attention throughout.

NOTES

Royal College of Physicians of Edinburgh

A QUARTERLY Meeting of the College was held on Tuesday, 6th November, the President, Dr A. Fergus Hewat, in the Chair. Dr A. J. Murray Drennan (Edinburgh) and Dr William Forbes (Edinburgh) were introduced and took their seat as Fellows of the College.

Dr Angus MacNiven (Glasgow), Dr J. S. Fulton (Glasgow) and Dr W. D'A. Silvera (Jamaica, B.W.I.) were elected Fellows of the College.

The Hill Pattison-Struthers Bursary in Anatomy and Physiology was awarded to Mr David Bull.

Royal College of Surgeons of Edinburgh

AT the annual meeting of the College, held on 17th October 1945, the following Office-Bearers were elected for the ensuing year: — *President*, Mr James M. Graham; *Vice-President*, Professor Robert William Johnstone, O.B.E.; *Secretary and Treasurer*, Mr K. Paterson Brown; *President's Council*, Principal Sir John Fraser, BART., Dr G. Ewart Martin, Mr Francis E. Jardine, Mr W. Quarry Wood, Mr Walter Mercer, Professor J. R. Learmonth. *Representative on the General Medical Council*, Mr Henry Wade, C.M.G., D.S.O. *Convener of Museum Committee*, Mr W. Quarry Wood. *Librarian*, Dr Douglas Guthrie.

At a meeting of the Royal College of Surgeons of Edinburgh, held on 17th October, Mr James M. Graham, President, in the Chair, the following who passed the requisite examinations were admitted Fellows: John Boyes, L.R.C.P. AND S.EDIN. (TRIPLE) 1936; Alan Elmslie Bremner, M.B., CH.B. UNIV. ST ANDREWS 1938; James Alexander Chalmers, M.B., CH.B. UNIV. EDIN. 1934, M.D. EDIN. 1944; Alfred Williams Chambers, L.R.C.P. AND S.EDIN. (TRIPLE) 1942; Prudence Halton, M.B., B.S., UNIV. LOND. 1942; Justo Arturo Harpman, M.B., B.S. UNIV. LOND. 1940; George Hay, M.B., CH.B. UNIV. EDIN. 1938; William Alexander Nelson Inglis, M.D. UNIV. ALBERTA, CANADA 1937; Eric Milner Innes, M.B., CH.B., UNIV. ABERDEEN 1940; Alberta Muriel Jeans, M.R.C.S. ENG., L.R.C.P. LOND. 1940; Kathleen Mary Long, M.B., B.S. UNIV. DURHAM 1940; Robert Noel Martin, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1937; Douglas Telford, M.D. UNIV. TORONTO 1933, L.M.C. CANADA 1933; Norman Whalley, M.B., CH.B. UNIV. MANCH. 1937.

Triple Qualification Board

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG.:—Mostafa Amin, James Batchelor, Ernest Jackson Bates, George Henry Ferguson Beith, Cyril Kenneth Black, Richard Burns, Wilfrid Keane Christopher, Samuel Joseph Gelman, Jacob Noel Gould, John Alexander Gowans, Hilda Granat, David Groad, Samuel Hillman, Llewelyn Bunner Pugh Jones, Herman

Robert Levine, Siew Gek Loh, Dominic William Andrew McCreadie, Ian Alexander MacGregor, Andrew Bruce Mackenzie, Andrew Alexander Robertson Meek, Atholl Scott Mitchell, Abdulla Moselhi, Francis Anderson Murray, William Marchant Murray, Sidney Ronald Orens, Alan Charles Parry, Alberto Giovanni Pollacchi, Margaret MacLeod Roake, James Neequaye Robertson, David Oliver Stonewall-Payne, Walter Robert Taylor, Youssef Ezzat Zaki; and the following graduate of a recognised foreign University was also admitted a Licentiate:—Leon Nabel, M.D. UNIV. PRAGUE.

NEW BOOKS

Manual of Nutrition. By MAGNUS PYKE. Pp. iv+64. London: H.M. Stationery Office. 1945. Price 1s.

This small book has been written to explain the principles of the science of nutrition to the lay public, especially to those who may already possess a practical knowledge of catering. The earlier part of the book describes the primary elements of food—carbohydrates, fats, proteins, salts and vitamins. A short account is then given of the digestion, absorption and ultimate fate of the nutrients in the human body. Other chapters deal with nutritional requirements, cooking, meals and diets. There are numerous tables showing the distribution of various elements of the food.

The book is excellently written and gives a good account of the subject. It should be of the greatest value to anyone interested in human nutrition.

Index of Modern Remedies. Third Series. By WILLIAM MAIR, F.R.S.E., F.C.S. Pp. 67. Glasgow: *The Scottish Chemist.* 1945. Price 2s.

This useful little book makes a welcome appearance. The new edition should have an enhanced value as it now offers a classified arrangement and an excellent index for convenience of reference. It includes the newer medicaments of the various Addenda to the B.P. and the B.P.C. and a vast number of proprietary substances. Mr Mair has done a valuable service to the profession, and we feel that this work will meet the reception it deserves.

Bone-Grafting in the Treatment of Fractures. By J. R. ARMSTRONG, M.D., M.CH., F.R.C.S., with a Foreword by R. WATSON-JONES, B.SC., M.CH.(ORTH.), F.R.C.S. Pp. xii+175, with 204 illustrations, several in colour. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 25s. net.

This new work is a worthy successor to that of Albee. Armstrong alludes to the fact that in standard text-books very little space is allotted to the application of bone-grafting in the treatment of fractures. In this work the subject is treated in great detail, particularly as regards the operative technique and the pre-operative and post-operative management, but throughout the descriptions are as simple and practical as possible.

There is an interesting chapter on the types and sources of grafts. The author visualises in the future at each orthopædic centre a "bank of stored bone." There is a clamant need for some research work here—more looking to the future and less joiner work.

The book is beautifully produced, but one wonders whether the colour illustrations are worth while, since they show rather less than a good black and white photograph, and in any case the colours are hardly true in their reproduction. The work is an excellent one, though it is doubtful if it adds anything new to our knowledge.

NEW EDITIONS

Manual of Psychological Medicine. By A. F. TREDGOLD, M.D., F.R.C.P. Second Edition. Pp. 308. London: Baillière, Tindall & Cox. 1945. Price 18s. net.

A second edition of this small book so soon after the first is a good indication of the growing interest in psychiatry. The form and content of the book are essentially unchanged, but small additions have been added to keep it in line with present-day methods and practice. Perhaps one of the most interesting features is the strong plea for the development of facilities in relation to early treatment, and to the training of the general practitioner.

In relation to the causation of schizophrenia the author is not very sure of his ground, but taking the book as a whole it may be described as a safe and satisfactory summary of the subject.

Textbook of Gynæcology. By WILFRED SHAW. Fourth Edition. Pp. viii+636, with 4 plates in colour and 271 text-figures. London: J. & A. Churchill. 1945. Price 24s.

In preparing this edition the author has made a careful revision of the text. New work in endocrinology, chemotherapy and diseases of the ovaries has been incorporated and sixteen new diagrams have been added. Throughout, every effort is made to relate disordered physiology and pathology to clinical features and thus indicate the rationale of modern treatment. By so doing the student is given a logical presentation of the subject, as far as this is possible, while deficiencies in present knowledge requiring further elucidation are indicated.

Easy to read, students and practitioners will find this a useful and concise textbook of modern gynæcology.

BOOKS RECEIVED

BARNARD, W. G., F.R.C.P., and A. H. T. ROBB-SMITH, M.A., M.D. Kettle's Pathology of Tumours. Third Edition. (*H. K. Lewis & Co. Ltd., London*) 21s. net.

EVANS, C. LOVATT, D.SC., F.R.C.P., F.R.S., LL.D. Principles of Human Physiology. Originally written by Prof. E. H. STARLING, M.D., F.R.C.P., C.M.G., F.R.S. Ninth Edition . . (*J. & A. Churchill Ltd., London*) 36s. net.

GLAISTER, JOHN, J.P., D.SC., M.D., F.R.S. (ED.). Medical Jurisprudence and Toxicology. Eighth Edition (*E. & S. Livingstone Ltd., Edinburgh*) 30s. net.

HERRMANN, GEORGE R., M.D., PH.D. Clinical Case-Taking. Guides for the Study of Patients. Third Edition . . (*Henry Kimpton, London*) 9s. net.

PANTON, P. N., M.A., M.B., B.CHIR. CANTAB., J. R. MARRACK, M.A., M.D. CANTAB., and H. B. MAY, M.A., M.D. CANTAB., M.R.C.P. Fifth Edition . . . . . (*J. & A. Churchill Ltd., London*) 21s. net.

ROSS, J. COSBIE, M.B., CH.M., F.R.C.S. Essentials of Surgery for Dental Students . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 20s. net.

WRIGHT, SAMSON, M.D., F.R.C.P. Applied Physiology. Eighth Edition. (*Oxford University Press, London*) 31s. net.

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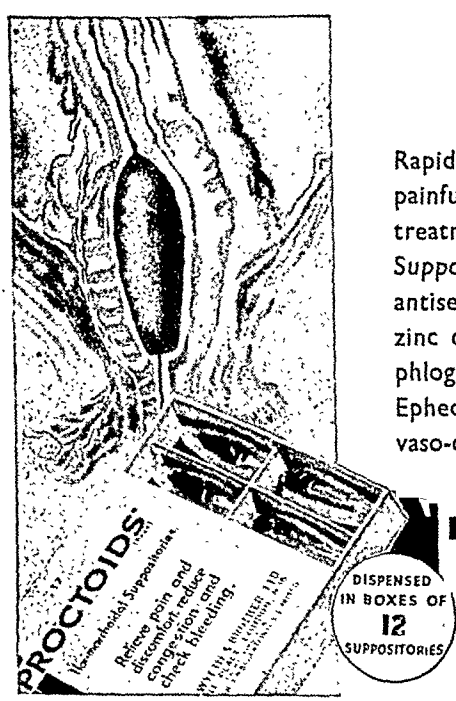

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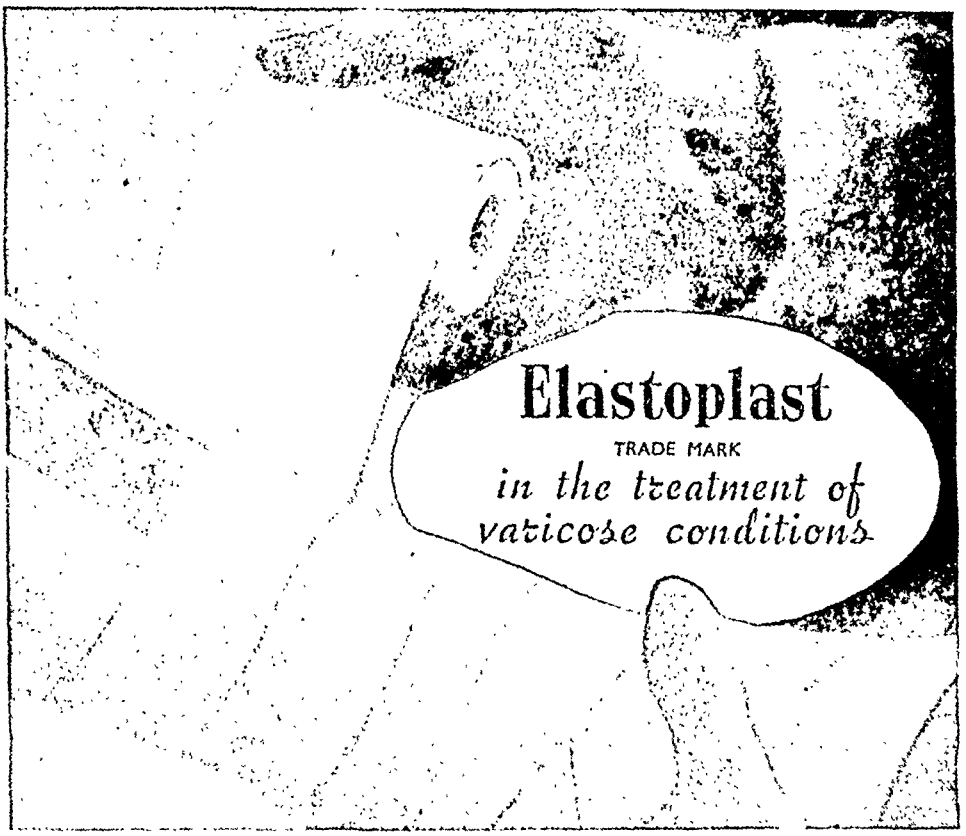

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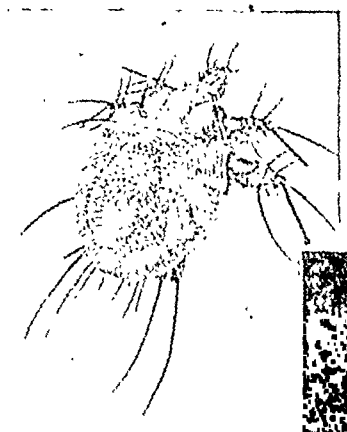

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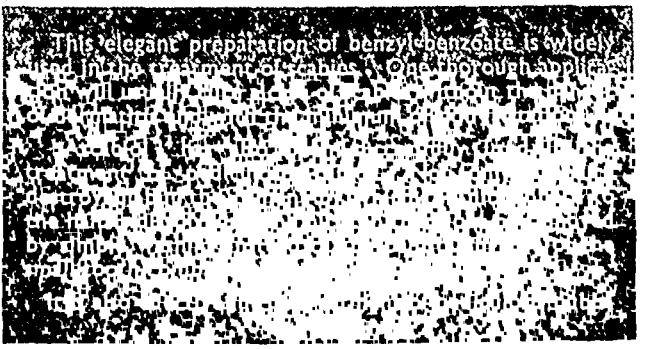

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Edinburgh Medical Journal

December 1945

THE TREATMENT OF DUODENAL ULCER *

By W. QUARRY WOOD, M.D., CH.M., F.R.C.S.E.

THE problem of peptic ulceration continues to excite universal interest and to become of increasing importance. The obscurity of its causation, the serious disability and suffering which it often produces, the danger to life with which its complications are associated, and the frequently unsatisfactory results of treatment—all make it a subject which is worthy of our most serious consideration. It is a common disease and is steadily increasing in frequency as is shown by the steady rise in mortality. There were 43,000 deaths in England and Wales in the ten years before the war as the result of peptic ulceration. The number of men discharged from the army in the present war up to December 1941—a little over two years—on account of peptic ulceration was 23,574. It is estimated that there are nearly 200,000 fresh cases each year in England and Wales in males alone. Professor Illingworth and his colleagues have shown that the frequency of perforation in the hospitals of the West of Scotland had more than doubled in the period between 1924 and 1941. In view of this general rise in the incidence it seemed worth while to enquire into the position in the hospitals in this area. Table I shows the number of perforated ulcers

TABLE I

Perforated Ulcers

	1930-31.	1931-32.	1932-33.	1933-34.	1934-35.	1935-36.	1936-37.	1937-38.	1938-39.	1939-40.
Royal Infirmary	153	127	124	127	132	127	123	185	186	158
Leith Hospital .	9	18	15	12	10	14	7	16	18	17
Western General Hospital	...	...	2	5	2	4	2	6	6	3

in the Royal Infirmary over the ten-year period 1930-1939. Through the kindness of Mr David Band I have been able to include the cases admitted to Leith Hospital for the same period, and to the Western

* A Honyman Gillespie lecture delivered in the Royal Infirmary, 14th June 1945.

General Hospital from 1933 onwards. A certain number of cases have been operated on in the other hospitals in this area and in nursing homes, but the factors governing admission to hospital did not alter seriously during that period, and these figures give a fairly accurate guide to the incidence of perforations in the area. The result is rather surprising. You will see that although there have been fluctuations from year to year there has been no significant change over the whole period. The number of cases in the Royal Infirmary during the first year was 153 and during the last year 158. The figures for Leith Hospital and the Western General Hospital also fail to show the steady increase which has been noted elsewhere. It is interesting to notice that the highest incidence in all three hospitals was about the time of Munich, when the threat of war became apparent to most of us for the first time. I do not know why this area should have escaped the general rise in the incidence of perforation. The industrial population, especially in Leith, must have been exposed during this time to very much the same factors as regards anxiety or under-nourishment as the population of Glasgow.

I have also obtained the figures for admissions to the Royal Infirmary of cases of duodenal ulcer other than perforations, both on the medical and on the surgical sides, over the same ten-year period. Table II shows that there has been a considerable reduction in the cases admitted to the surgical side and this conforms to recent trends

TABLE II

Admissions to Royal Infirmary

	1930-31.	1931-32.	1932-33.	1933-34.	1934-35.	1935-36.	1936-37.	1937-38.	1938-39.	1939-40.
Medical Side .	199	156	166	181	170	154	213	183	201	159
Surgical Side .	158	151	126	143	135	103	89	96	44	51

in treatment. We might have expected this to be counterbalanced by an increase in the admissions on the medical side, but this has not taken place. It should be kept in mind, however, that figures for hospital admissions for non-urgent cases do not give a true picture of the incidence or seriousness of a particular disease. Pressure on hospital beds is such that ulcer cases may have had to be denied efficient treatment on account of the necessity to admit more urgent conditions.

Etiology of Duodenal Ulcer

Before discussing the question of treatment, it is necessary to consider briefly the etiological factors concerned in the production of duodenal ulcer, so far as these are known; it is difficult to carry out a rational form of therapy where the fundamental cause of a lesion is in doubt. We are compelled to admit, in the case of duodenal ulcer,

that we are still ignorant of the essential cause of this disease. It is generally believed that there are at least two factors concerned; one of these is thought to be the digestive action of the acid gastric juice and it is on this belief that our methods of surgical treatment are founded. The other, the unknown factor, still remains in the realms of speculation. It is generally assumed that this unknown factor lowers the vitality of the duodenal mucosa so that it succumbs to the digestive action of the gastric juice and that the gastric juice perpetuates the ulcer once it has been established. Many suggestions have been made as to what this hypothetical factor may be—trauma to the mucous membrane from contact with irritating food, infective lesions, local or embolic, the action of bacterial or non-bacterial toxins, or the lack of essential vitamins.

There seems little doubt that the first factor, the acid gastric juice, must play an important part. Peptic ulcers are limited to those parts of the alimentary canal which are exposed to the action of gastric juice—the stomach, the duodenum, and the jejunum after a gastro-jejunostomy. They have been met with in the intestine in relation to a Meckel's diverticulum, but their occurrence in this situation is explained by the presence in the diverticulum of heterotopic gastric mucous membrane containing acid-producing glands. In peptic ulceration of the lower end of the œsophagus the explanation is probably the same. It is stated that peptic ulceration has never been met with in a case of achlorhydria.

Experimental evidence strongly supports the belief that the presence of acid gastric juice is an essential factor in the production and chronicity of gastric and duodenal ulcers. During the past twenty years, as a direct result of planned experimental procedures, the disease has been produced in many different animals and is found to resemble in almost every particular the condition encountered in man. It seems likely, therefore, that an accurate understanding of the alterations in the physiology of the alimentary tract under which experimental ulcer forms and heals should largely clarify the clinical problem. In the Mann-Williamson operation of "internal duodenal drainage" the upper part of the intestinal tract is subjected to the action of acid gastric juice by diverting the alkaline neutralising secretions, *i.e.* the bile, the pancreatic juice and the intestinal secretion. The pylorus is divided and the proximal end of the duodenum closed; the upper end of the jejunum is divided and the proximal end with the duodenal secretions is united to the terminal ileum, the distal end of the divided jejunum being united to the stomach. This procedure results in the production of chronic ulcer of the jejunum immediately beyond the junction with the stomach in practically all cases. When the duodenal secretions are diverted into the stomach immediately proximal to the anastomosis, as in the operation of Graves, so as to neutralise the acidity of the gastric juice, the ulceration of the jejunum is completely prevented.

Although antecedent devitalisation of the mucosa has usually been postulated as necessary to pave the way for the action of the gastric juice, doubts have now arisen on this point. The chemical and mechanical trauma produced by the normal stomach contents are not sufficient to induce lesions in the normal gastric and duodenal mucosa and prevent them from healing or indeed to delay materially the healing of extensive lesions artificially produced. Important evidence has recently been accumulating which suggests that peptic ulceration may be due to the action of the gastric juice alone without the antecedent or associated action of any other factor. The problem as to why the stomach does not digest itself excited the wonder of John Hunter among many others. He attributed it, in picturesque language, to some inherent property of living tissue: "If one could conceive a man to put his hand into the stomach of a lion, and hold it there without interfering with the digestive powers, the hand would not in the least be digested; and if the hand of a dead man was put in at the same time, whether separated or not from the body, that hand would be digested while the other would not." Dragstedt has shown experimentally that living tissues have considerable resistance to the gastric juice of the normal stomach contents. He has reproduced the picture of Hunter by implanting isolated segments of duodenum, jejunum, ileum and colon into a defect in the stomach. If the blood supply to the implanted segments is carefully preserved they resist the action of the gastric juice. So also does the spleen, kidney and pancreas introduced into a defect in the stomach wall in the same way. This observer has shown, however, that pure gastric juice has the power to digest and destroy all living tissues, including the wall of the stomach itself. Under normal conditions the gastric wall is not digested away because it is not exposed to pure gastric juice, the gastric juice being neutralised and diluted by swallowed food, water and saliva, by the secreted mucus, especially of the pyloric antrum, and by regurgitated duodenal contents. Food, which in normal subjects is the stimulus for the formation of gastric juice, is also the chief factor which protects the tissues against its corrosive activity. The acidity of pure gastric juice is approximately 0·5 per cent., but that of the gastric contents is only 0·1 per cent. Pure gastric juice is obtained experimentally from a Heidenhain or a Pavlov pouch. Matthews and Dragstedt showed that when such a pouch was drained into the jejunum or the ileum instead of to the outside a large progressive perforating ulcer developed in the intestinal mucosa adjacent to the anastomosis with the accessory stomach in 85 per cent. of instances in the jejunum, and in 100 per cent. in the ileum. This experiment reproduces the conditions in which peptic ulcer develops in relation to a Meckel's diverticulum. Important observations have been made by Varco and Code and their co-workers in the University of Minnesota on the prolonged action of histamine in the experimental animal. This substance is a powerful stimulant of gastric secretion.

By giving daily injections of a combination of histamine and beeswax they were able to produce a continuous profuse secretion of gastric juice over the twenty-four hours for a prolonged period. The effect of this continuous secretion was to bring about the formation of both gastric and duodenal ulcers, and these experimental ulcers were produced in a large variety of animals, including pigs, calves, ducks and chickens, as well as the commoner experimental animals. These ulcers resulted from the prolonged continuous action of the gastric juice, and it is important to note that there was no question of trauma to the mucous membrane, other than the normal frictional trauma of the food, or of any other form of antecedent devitalisation. These investigators consider that the observation lends strong support to the thesis that acid is the important factor in the genesis of spontaneous ulcer in man. The predominating action of histamine on the gastric mucosa is the stimulation of the acid-producing cells; it does not stimulate secretion of pepsin to the same degree.

In order to relate these observations to the condition met with clinically, it is necessary to refer here briefly to the mechanism and control of gastric secretion. The mucous membrane contains four types of cell—surface, mucoid, peptic and oxyntic. The surface cells cover the inner surface of the mucosa and line the ducts of the tubular gastric glands; they secrete mucus. Mucoid cells form the secreting cells of the pyloric and cardiac glands; these glands secrete an alkaline mucus which must play an important part in regulating gastric acidity. Oxyntic cells are concerned in the production of hydrochloric acid and peptic cells in the production of pepsin; they are present over a wide area of the stomach including the body and fundus. The digestive period of gastric secretion is conveniently divided into three phases—the cephalic, the gastric and the intestinal. The cephalic phase is provoked by stimuli such as the thought, smell, sight or taste of food. The vagi are the efferent nerves of the cephalic phase, since section of these nerves will abolish this phase of secretion. The gastric juice of the cephalic phase is highly acid and possesses considerable peptic activity. The gastric phase of secretion is due to a chemical mechanism. Certain chemical substances are present in meat and are produced in various other foods under the action of the gastric juice of the cephalic phase. These substances are believed to act on the mucous membrane of the pyloric segment of the stomach and cause the formation of a hormone—gastrin—which is absorbed into the blood stream and carried to the glands of the stomach, where it acts as a specific excitant of their secretory activity. The intestinal phase of gastric secretion is provoked by the presence of similar substances in the intestine.

The empty or fasting stomach usually secretes a small amount of gastric juice which is referred to as the interdigestive or continuous secretion. The normal rate of this secretion in man is said to be between 15 and 117 c.c. per hour. The small volume permits almost

complete neutralisation by the mucus of the pyloric antrum, swallowed saliva and possibly also regurgitated duodenal juices. It is conceivable that this neutralising mechanism may fail or prove inadequate in various ways, and that as a result more or less pure gastric juice may accumulate in the stomach empty of food. It seems possible that some physiological disturbance of this type is responsible for most of the cases of ulcer in man. There is some evidence that an excessive volume of gastric juice is secreted by many, perhaps most, patients with ulcer, although the cause of the hypersecretion is unknown. It is said that the ulcer patient secretes more gastric juice in response to a meal than the normal person and also, what is perhaps more important, that he secretes more gastric juice when there is no obvious stimulant. In one series of observations the stomach was washed out in the evening and continuous aspiration maintained all night. In patients with duodenal ulcer 500-1200 c.c. of fluid were withdrawn with free acid that in one case reached 90 clinical units; in normal subjects the amount was usually less than 300 c.c., and free acid was rarely above 50 clinical units, often entirely absent. What would account for a hypersecretion of gastric juice in the human subject? In recognising an ulcer diathesis or constitutional predisposition, we imply that a certain type of subject is specially liable to suffer from peptic ulcer. The highly strung, nervous, energetic patient, exposed to mental or physical strain, is more liable to develop a duodenal ulcer than one of placid temperament who leads a quiet life. Nicol, in reporting on relapse of symptoms in cases of duodenal ulcer, states that a definite factor of mental or psycho-physiological strain was present in 43 per cent. of the patients. During the worst period of the air bombardment of London there was a very marked rise in the number of cases of perforated ulcer, suggesting that mental strain or anxiety plays an important part in the development of ulcer. In 1931 Cushing made the observation that certain cerebral tumours were occasionally associated with ulceration of the stomach. This observation has been made repeatedly since then. In patients who have died from the acute complications of peptic ulcer, hæmorrhages have been described in the anterior part of the hypothalamic region, and this appears to be the part of the brain with which the nervous mechanism of the stomach is linked. It has been shown experimentally that damage or stimulation of the hypothalamic region may be followed by hæmorrhage, erosion, or even perforation in the stomach or duodenum. The ulcer which occurs in the duodenum after severe burns has generally been considered to result from devitalisation of the duodenal mucosa by toxic substances absorbed from the burned area, but Christophe has shown experimentally that after severe burns a substance is carried by the blood which seriously injures the hypothalamic nuclei. The animals later developed acute gastric hæmorrhages and erosions. Thus, both clinical observation and animal experiment strongly support the view that a neurogenic factor is

concerned in the production of duodenal ulcer. It may be that the nervous factor brings about an increase in the secretion of gastric juice, especially in the inter-digestive period.

From the point of view of treatment, although numerous other factors are no doubt involved in the causation of duodenal ulcer, such as dietetic errors, the abuse of tobacco and so on, it seems reasonable to lay most emphasis on the control of gastric secretion and on the elimination of the factor of nervous strain, if this is possible.

Methods of Treatment

The treatment of duodenal ulcer has passed through several phases during the past twenty years. At the beginning of this period the pendulum had swung far over to the side of surgery, mainly in the form of gastro-enterostomy. When the unfortunate late complications of this operation became apparent, a reaction took place in favour of medical treatment and this has persisted since. Certain decisions seem now to have been reached, and I should like to refer to four points of view which are widely held. These are :—

(1) The treatment of the uncomplicated duodenal ulcer is a medical problem, not a surgical.
(2) Gastro-enterostomy in the absence of well-marked organic stenosis is a bad operation and is universally condemned.
(3) In the presence of well-marked organic stenosis gastro-enterostomy is a safe procedure and gives good results.
(4) In a case of duodenal ulcer without stenosis where operative treatment is indicated, an extensive partial gastrectomy (sub-total gastrectomy) is the only justifiable procedure.

I should like to consider each of these points a little further.

(1) *Medical Treatment.*—With the first of these, that the treatment of the uncomplicated duodenal ulcer is a medical problem, no one will disagree. The details of medical treatment have varied from time to time and I am not competent to discuss these, but there seems to have been a tendency recently to lay more stress on an initial period of complete mental and physical rest than on the details of medicinal and dietetic measures. The great majority of patients—about 80 per cent.—are able to live in reasonable comfort, if they eat properly, eliminate alcohol, tobacco and condiments, and avoid worry and strain. There are certain cases which present special difficulty. The application of medical treatment in the hospital patient is particularly difficult owing to lack of hospital accommodation and the impossibility, in many cases, of carrying out a proper dietetic regime when the patient returns to his own home. Many patients find that they are well when they can rest and stick to their diet, but when they return to work the symptoms recur. If a man is to retain his self-respect, especially if he has a family to support, he must stick to his job. It is easy to

advise him to change his occupation, but in many cases this is quite impracticable. This type of case forms a special problem and the economic factor may tip the scales in favour of surgical treatment, not on account of the failure of medical measures, but on account of the impossibility of their proper application. Another difficulty arises when medical treatment, after a thorough and prolonged trial, fails to relieve the patient's symptoms or where frequent relapses take place. A further problem is the type of patient who has not enough self-discipline to obey the rules, especially as regards alcohol and tobacco; he does not deserve much sympathy and is certainly not a good candidate for surgical treatment.

It must be admitted that, so far as complete cure of the ulcer is concerned, the results of treatment, both medical and surgical, are, as yet, far from satisfactory. Nicol carried out an investigation under the direction of Professor Davidson on a series of 435 cases of peptic ulcer treated in the Aberdeen Royal Infirmary between 1927 and 1936. Three hundred and eighty-seven of these cases were traced and re-examined; 54 were gastric and 333 duodenal. The late results of both medical and surgical treatment were found to be disappointing. He found that 73·6 per cent. of patients after medical or surgical treatment in hospital are temporarily "cured." After an interval of between two and twelve years, only 16·8 per cent. were found to remain "cured," and a further 41·1 per cent. were found to be "improved," *i.e.* better than before treatment but still suffering from dyspepsia if not careful with their diet. These results were much the same with both medical and surgical treatment. I ought to mention that, out of 109 cases treated surgically, in only 12 was a partial gastrectomy performed, so that these results, so far as surgical treatment is concerned, are not strictly comparable with those of some other centres. This investigation of Nicol's seems to me of great importance and should certainly remove any feeling of complacency as regards the results of treatment of this disease.

(2) *Gastro-enterostomy in the Absence of Stenosis.*—It has long been realised that gastro-enterostomy is an unsatisfactory operation in non-stenosing duodenal ulcer owing to the frequency of secondary ulceration. In young patients with a high acidity of the gastric juice and with no stenosis, the incidence of stomal or jejunal ulceration has undoubtedly been very high; some observers place it as high as 15 to 20 per cent. This complication is so dangerous and so difficult to treat when it arises that gastro-enterostomy is to be regarded as obsolete in this type of case. Apart from this complication the operation has given good results in the past and may not entirely deserve the condemnation which it has almost universally received. There is still a place for this operation, even in the absence of stenosis, in a few special cases, particularly in the elderly patient who is an unsuitable subject for partial gastrectomy and in whom the acidity of the gastric juice is nearly always low. In a recent paper, Lahey has stated that

he employs this operation, apart from cases of cicatricial stenosis, in those patients in whom medical treatment has failed and who are poor subjects for gastrectomy on account of hypertension, a cardiac lesion or some other disability. He modifies the operation in such a way that, if a secondary ulcer should develop, it will be comparatively easily dealt with.

In the absence of stenosis, the indications for gastro-enterostomy are very rare, but in the exceptional cases mentioned it may still serve a useful purpose.

(3) *Gastro-enterostomy in Cicatricial Stenosis.*—It is generally believed that in a true organic stenosis resulting from duodenal ulcer gastro-enterostomy gives satisfactory results. Nicol, in the paper to which I have referred, found that the results of this operation in the presence of cicatricial stenosis were better than those obtained in any type of case by any other form of treatment, medical or surgical. Although this opinion is widely held and is correct up to a point, I do not think it can be accepted without certain reservations. I can recall more than one personal case where jejunal ulcer has developed after gastro-jejunostomy in the presence of well-marked stenosis. In most cases of long-standing stenosis the acidity of the gastric juice is low, probably as the result of an atrophic gastritis; in these cases gastro-jejunostomy is safe and eminently satisfactory. In exceptional cases, even with a well-marked stenosis, the acidity of the gastric juice may still be high; the risk of jejunal ulcer after gastro-jejunostomy in such a case must be just as great as in a case without stenosis. It is obviously essential to have the most careful examination of the gastric secretion carried out before gastro-jejunostomy is performed, however striking the evidence of stenosis may be. It should also be kept in mind that, though the acidity may be low when the patient first comes under observation, this may be due to associated mild gastritis which clears up under treatment by lavage and other measures and the acidity may then rise considerably. It is therefore necessary to carry out repeated examinations of the gastric juice. If the acidity is high or rises after treatment, gastro-enterostomy is not permissible even with well-marked organic stenosis and some other operation must be performed.

(4) *Operative Treatment in the Absence of Stenosis.*—In the absence of stenosis, operation is sometimes indicated on account of repeated hæmorrhages or the intractability of the symptoms. The fourth opinion which I mentioned as having gained general acceptance was that, in this type of case, the only justifiable operation is an extensive partial gastrectomy. The cases which require surgical treatment in the absence of stenosis are, of course, only a small proportion, but in cases of recurrent bleeding or of persistence of crippling pain after thorough and prolonged trial of medical measures, treatment by operation may be considered necessary. The operation of partial gastrectomy has been much more widely practised in the past on the

Continent than in this country, and it is only in the last ten or fifteen years that it has become established here. In the Mayo Clinic this operation is now performed on nearly half the duodenal ulcer patients who come to operation, whereas eight or nine years ago it constituted less than 10 per cent. of the operations for duodenal ulcer. At the same time a larger proportion of duodenal ulcer patients in the Clinic are being treated medically, so that the average severity of the disease in those patients reaching the surgeon is greater and is held to justify the more dangerous procedure. The aim of the operation is to bring about a permanent reduction of the acidity of the gastric juice so as to guard the patient from further trouble. The permanent reduction in acidity is brought about by removal of a large proportion of the acid-secreting segment of the stomach, by removal of the mucous membrane of the pyloric segment which is the main source of the hormone, gastrin, concerned in the chemical phase of gastric secretion, by permitting more ready regurgitation of the alkaline intestinal secretions and by reducing the emptying time of the stomach. If it can be done with reasonable safety, the ulcer-bearing part of the duodenum is removed at the same time. In order to reduce the possibility of secondary ulceration to a minimum there has been a tendency to remove more and more of the acid-secreting part of the stomach, and most authorities now consider it advisable to remove about two-thirds. Some go a little further and advise removal of three-fourths. This is a formidable procedure and a careful consideration of its effects on the patient and of its difficulties and dangers is necessary. It has been stated by Roscoe Graham that the patient who accepts operative treatment expects (1) recovery from the operation, (2) relief from the symptoms, (3) security against recurrence of the disability, and (4) restored economic efficiency. It is claimed that gastrectomy fulfils these expectations, and I believe that as regards relief of symptoms, security against recurrence and restored efficiency, these claims are largely justified. Maingot states that "the final results leave little to be desired and fully 90 per cent. of the patients are restored to full economic efficiency." Even this drastic operation is not a complete safeguard against jejunal ulcer, though this complication is rare—probably not more than about 2 per cent. (Maingot).

It is the first condition stated—that the patient should recover from the operation—that requires discussion. Many series of cases have now been published with a remarkably low operative mortality, some of less than 2 per cent. Pannett had only one fatality in 116 operations—a mortality of 0·86 per cent. These results, however, are only achieved under the most favourable conditions of expert team work and technical skill. The average mortality must be considerably higher. I should like to quote the views of Lahey who, I need not say, is one of the leading authorities in America on abdominal surgery. In a paper by himself and Marshall in 1939 he states: "There has been no operation in our experience in which it has been more difficult

for us to overcome complications and in which it has been more difficult to reduce mortality than in that of subtotal gastrectomy. It seems to us that there is no operation in which a relatively large experience and frequent practice are more important and more necessary than in that of subtotal gastrectomy if the mortality rate is to be reduced and kept low. There is no operation with which we have had experience in which co-operation between gastro-enterologists in the preparation of the patient and in the management of the active stage of the ulcer before coming to surgery is more necessary than in this one. Certainly there is no operation in surgery in our experience in which the type of anæsthesia plays a greater part not only in relation to the ease with which the operation can be done but more particularly to complications, such as pulmonary complications, wound infections and obstruction after operation." Previous to September 1938 they had performed 200 subtotal gastrectomies. Up to two and a half years before publication of this report the mortality was 18 per cent. In the period from two and a half to one and a half years previously the mortality dropped to 11 per cent. During the year and a half before publication there were 151 consecutive cases without a death. These remarks from a man of Lahey's ability and experience are a good indication of the light in which this operation should be regarded and of the ways in which its dangers may be reduced as much as possible. Morley considers the mortality of gastrectomy in duodenal ulcer to be 6 per cent. In a recent paper Hinton gives his mortality as 5 per cent. A leading article in the *Lancet* in 1942, in which the writer is advising the family doctor on the handling of cases of duodenal ulcer, after referring to the brilliant results in the Mayo Clinic, states that these results are only to be obtained under special circumstances and that the practitioner will be wise to assume a 5 to 10 per cent. mortality.

If this operation is to be generally employed as the surgical treatment for duodenal ulcer, every effort must be made to diminish its dangers and to lower the operative mortality. This can only be achieved by the most careful collaboration between the physician, the surgeon, the anæsthetist, and the nursing staff before, during and after the operation. It is a typical illustration of the kind of operation where team work makes all the difference between good and bad results. It is encouraging and stimulating to make a comparison with the operation of subtotal thyroidectomy for toxic goitre. The circumstances in which the two operations are called for and the type of operative procedure carried out show certain resemblances. In the early days of thyroid surgery, when surgical treatment was carried out as a last resort, the operative mortality was dreadful. As a result of improvements in the pre-operative preparation of the patient on the part of the physician, of improvements in methods of anæsthesia, and of increasing skill and experience on the part of the surgeon, the mortality of the operation has been reduced to a very low figure, as has been well demonstrated by Mr J. M. Graham.

In considering the position of partial gastrectomy in the treatment of this disease the question arises as to what handicaps and penalties, if any, attend the removal of two-thirds or three-fourths of the stomach. The chief functions of the normal stomach are to store food, to mix it thoroughly with gastric juice, which commences the breakdown of food constituents by ferments and dissolves the mineral constituents of the food, and the rhythmic delivery of the partly digested food in a semi-fluid form into the duodenum. Fears have been expressed that the loss of such important parts as the pyloric sphincter, the pyloric antrum, and the active motor part of the stomach, the loss of most of the gastric juice and the neutralisation of any remaining hydrochloric acid by regurgitating intestinal fluids would lead to serious disturbance of gastro-intestinal digestion and possibly to nutritional changes and deficiency states later on. It must be admitted that our knowledge of how digestion is carried on after gastrectomy and the effect of this operation on the organism as a whole is very incomplete. One of the most remarkable facts about partial gastrectomy is the complete absence of any handicap as regards the actual taking of food. We find, as a rule, that within four months of operation the capacity of accommodating food in the majority of the patients has returned to normal and they are able to take a full-sized meal. They are able to take ordinary food and no dietary restrictions are necessary. This is explained by the fact that the portion of the stomach which remains is the most easily dilatable part, and also by the fact that the upper coils of the jejunum undergo dilatation. Since removal of two-thirds or three-fourths of the stomach leads to complete achlorhydria, digestion in the stomach practically ceases. Albumins and fats are not reacted on chemically during their stay in the remnant of the stomach. Pepsin digestion is completely absent, while trypsin enters the stomach through the stoma only in traces. Chemical treatment of the food begins when the food enters the upper dilated coils of the jejunum and comes into contact with the duodenal secretions.

Fears have also been felt about the effect of the operation on the blood-forming organs as a result of the loss of the intrinsic anti-anæmic factor which seems to be mainly produced in the pyloric segment. Morley and others have described a microcytic anæmia as a sequel to the operation. It is possible that this has been due to dietetic deficiency and not to inability to make use of the food constituents. Roscoe Graham states that "We have not encountered a single case of anæmia which was not due to insufficient food or a badly balanced diet, the latter explained in many instances by economic stress. Such patients readily respond to a proper diet with iron therapy." This seems to be the view of most authorities. A macrocytic type of anæmia is said to be met with occasionally after the operation, but it is certainly very rare. Since a patient in whom a total gastrectomy has been performed does not necessarily become anæmic there must

be other sources of the intrinsic factor than the stomach. The risk of serious post-operative anæmia is very slight and cannot be regarded as a serious drawback to the operation. One further possibility must be considered. Hurst laid stress on the importance of the antiseptic action of the gastric juice as a safeguard against infection of the upper reaches of the abdominal alimentary canal. He pointed out that in achlorhydria the abnormally alkaline secretion of the contents of the duodenum affords a favourable medium for the growth of the *Bacillus coli* which invades not only the small intestine but also the stomach. The infection of the duodenum is of special importance, as it often leads, according to Hurst, to an ascending infection of the bile ducts and is responsible for many cases of cholecystitis. The loss of the acid antiseptic barrier of the stomach contents also permits infection of the small intestine by swallowed organisms in streptococcal infection of the teeth and tonsils. Camps has demonstrated the importance of the acid barrier as a protection against infection by typhoid, paratyphoid and cholera germs. In actual experience the loss of the antiseptic barrier of the gastric juice after gastrectomy does not seem to be of serious consequence; I am not aware of any evidence to show that patients after gastrectomy are more liable to infections of the alimentary canal than normal subjects.

It may be said that most of the fears about the harmful effects of this operation on the organism have, so far, proved to be unfounded, but our knowledge of the post-operative changes in these patients is still very scanty, and sufficient time may not have elapsed since the operation became widely practised in this country for its full effects to have become apparent. Much further investigation in this direction is required.

Alternative Operations

Many surgeons have been reluctant to adopt such a drastic procedure as partial gastrectomy for the treatment of such a comparatively limited lesion as duodenal ulcer—a lesion which is not a very serious menace to life and where the question of malignancy does not arise. Although it has proved to be the most successful method of surgical treatment so far evolved, many must feel that it is too severe and that it is only a temporary or makeshift expedient. A large number of alternative procedures have been tried out, and I propose next to refer to some of these.

Gastro-jejunostomy has been the most widely practised. It was claimed for this operation that it brought about healing of a duodenal ulcer by permitting the free reflux of the alkaline intestinal secretion and by reducing the gastric hypermotility and so placing the stomach in a state of comparative rest, so that the conditions are more favourable for healing of the ulcer. The immediate risk of this operation is slight and there is little doubt that it is frequently followed by healing of the duodenal ulcer, but, as we have seen, the risk of jejunal ulcer is great

and the operation has been discarded in the treatment of this disease except in certain special cases.

Operations at the pylorus, such as pyloroplasty or gastro-duodenostomy, also permit free regurgitation of the alkaline duodenal secretions and are theoretically less likely to be followed by secondary ulcer than gastro-jejunostomy since the duodenum is accustomed to contact with acid gastric juice. The late Sir David Wilkie practised the operation of gastro-duodenostomy for a considerable time. In reviewing 180 of his cases in 1929 he found that the results were excellent in 64 per cent., and that a further 25 per cent. were relieved though not quite cured. Later, he came to modify his opinion about the value of the operation on account of the high incidence of late post-operative sequelæ. These operations at the pylorus have not stood the test of time, and have been largely abandoned, partly at least on account of the frequency with which secondary ulceration has developed.

The method of *partial gastric exclusion* was suggested by Devine. In this operation the stomach is divided obliquely in the upper third, the distal divided end is closed and the proximal end united to the upper part of the jejunum. The method was devised especially for the callous ulcer on the posterior wall of the duodenum where resection would be difficult or dangerous. This procedure ensures complete rest to the ulcer and probably brings about its healing, but the operation has been followed by the development of jejunal ulcer in a remarkably high proportion of cases. One of my colleagues who has employed the method had an incidence of 33 per cent. in a comparatively small series. The explanation would appear to be that the mucosa of the antrum is not removed and, by producing gastrin, maintains an excessive secretion of gastric juice from the proximal segment of the stomach.

Partial Fundusectomy.—This operation, suggested by Connell and unfortunately named, consists in excising a large wedge-shaped segment, not from the fundus but from the body of the stomach, the object of this procedure being the reduction of the gastric acidity by removal of a large portion of the acid-secreting part of the stomach wall. Reports on the results of this operation are very scanty in the literature. Wangensteen has reported 13 cases of modified fundusectomy, 8 of which were combined with gastro-jejunostomy. The results in these cases were clinically satisfactory. The operation does not seem to have been widely practised and sufficient information is not available for us to form an opinion about its value.

Vagotomy.—Division of the vagus nerves will abolish the cephalic phase of gastric secretion and consequently reduce the total volume of secretion in response to a meal. The operation of vagotomy has been practised intermittently during the past twenty years or more. The success of the operation will depend on the relative importance of the cephalic phase of secretion before operation and also on the presence

or absence of other effects, advantageous or the contrary, of the division of the nerves. It has been demonstrated that the vagi are necessary for the maintenance of normal gastric tone and that the rate of evacuation of some foods from the stomach is retarded by vagotomy. This delay in the evacuation of the stomach would prolong the chemical phase of gastric secretion and might defeat the object of the operation. It must be kept in mind also that the division of the vagi at or above the level of the cardia will cut off the parasympathetic innervation of the other abdominal viscera which are supplied below this level.

Professor Illingworth in his recent Honyman Gillespie lecture reported the early results of this operation in 4 cases. He showed most graphically that in ulcer cases there is a striking exaggeration of the normal rhythmic contractions of the stomach and that the viscus is in a state of constant writhing activity. He found that after operation a state of almost complete immobility resulted and regarded this as favourable to the healing of the ulcer. He also found that the quantity of the gastric juice secreted in a given time was much reduced, though the level of the gastric acidity was not much affected. Other observers have reported less favourably on this procedure and have stressed the anatomical difficulties and the dangers of the operation.

Ligature of the Gastric Blood-Vessels.—A further method of reducing the acidity of the gastric juice has been described by T. H. Somervell. This consists in ligation of a large proportion of the blood-vessels of the stomach with the object of cutting down the blood supply to the acid-producing area; this procedure is supplemented by a gastro-jejunostomy for reasons which I shall discuss later. Somervell has had an interesting and romantic career. He took part in one of the Mount Everest expeditions and is one of the very few people in the world who have reached a height of 28,000 feet by their own exertions. This was not so very far from the summit, and the feat is all the more remarkable in that it was accomplished without the help of oxygen. I had the good fortune to hear him lecture on this expedition and, as a result, I have taken a special interest in his writings. He became a medical missionary in the south of India in a region where the natives are particularly liable to suffer from duodenal ulcer. He has written two important papers on this subject, published in this country, as well as a number of others in Indian journals, and has written several books for the lay public. At the time of publication of his last paper on duodenal ulcer he had performed 2000 operations for the treatment of this condition. His mortality for gastrectomy for duodenal ulcer has been 3 per cent., so that it cannot have been any grave dissatisfaction with his operative mortality that led him to change his methods of treatment. As an illustration of the thoroughness of his methods, I may mention that he carries out the radiographic examination of practically every case himself, and in following up his cases he has toured the country and carried out fractional test meals on patients collected at various centres. The operation which he now

performs for duodenal ulcer in place of gastrectomy, which he previously favoured, consists in tying about four-fifths of the arteries to the stomach, this procedure being supplemented by a posterior gastro-jejunostomy. This is done by tying four out of every five of the small vessels on the greater curvature; most of the vessels of the lesser curvature are ligatured, only two small arteries being left on this curvature. This is carried out on the anterior aspect first and then an opening is made in the transverse mesocolon and a similar proportion of vessels on the posterior aspect is tied, so that the blood-supply of the stomach is reduced to about one-fifth. He has called the procedure a physiological gastrectomy, but this expression has been used by Ogilvie and others in another sense so that it is unsatisfactory. Somervell maintains that the effect of ligature of the blood-vessels is to reduce the acidity promptly, whereas gastro-enterostomy alone takes many months to reduce the acidity to normal limits in a highly acid case. He states that the reduction in acidity is kept up for at least two and a half years, but considers it advisable to perform a gastro-enterostomy in addition to tying the vessels. The explanation which he suggests for the reduction in acidity is that either many of the oxyntic cells die and are not replaced, or that (unlike other organs where anastomotic vessels enlarge after main vessels have been tied or destroyed) the stomach has in any case such an over-adequate blood-supply that after four-fifths of the arteries have been tied the remainder are sufficient for most of the stomach's needs without having to dilate.

The question arises as to whether the reduction in acidity which Somervell describes may not be due to the gastro-enterostomy alone. He points out that, though a gastro-enterostomy reduces the acidity of the gastric contents eventually, it does not do so immediately. The object of tying the vessels is to tide over the danger period between the time of operation and the time by which gastro-enterostomy has produced its full effects. In a few cases he has been able to test the efficacy of ligation of vessels alone—without gastro-enterostomy. There were 3 cases with symptoms of duodenal ulcer and with a high acidity in which no ulcer was found at operation. He ligatured the arteries but did nothing more. In 2 out of the 3 cases there was a well-marked reduction in the acidity. The third case was unaffected by the arterial ligation; he thinks that probably not enough arteries were tied. He now considers that for a duodenal ulcer uncomplicated by a gastric one a gastrectomy is unnecessary and therefore undesirable, when its good results can be obtained so easily by this much simpler operation. He had performed the operation 150 times without a death at the time of publication of his most recent paper.

It seemed to me that this method should be given a trial, and I have carried out the procedure in selected cases since December 1942. Forty-two cases of duodenal ulcer have been treated in this way. In a considerable proportion of these cases, many of which came from the medical side, an organic stenosis was present, but in some there

was no stenosis. In the same period 14 cases of duodenal ulcer complicated by cicatricial stenosis have been treated by gastro-enterostomy alone; in these cases the acidity of the gastric contents was low and the operation was considered to be free from the danger of secondary ulceration. During this same period 26 gastrectomies, including one total gastrectomy, were performed, but only 8 of these were done for non-malignant conditions, mainly owing to the fact that we were anxious to try out this method of Somervell's. I am not in a position, of course, to make any statement about the real value of this procedure, as the cases are too recent and too few in number. It will be necessary to wait for another two or three years at least before any conclusion can be reached. As regards the immediate effects of the operation, a second test meal was carried out on some of the patients at an interval usually of ten days to a fortnight after operation. The records of the second test meal are available in 31 cases. I have classified the results as regards the reduction in the free hydrochloric acid under four heads—striking, moderate, slight and no reduction. In those cases classified as showing striking reduction there was a high acidity beforehand and this was reduced to a low figure, sometimes to zero. In the 31 cases in which the record of a second test meal was available, 12 cases were classified as showing a striking reduction in the gastric acidity; in two of these complete achlorhydria persisted throughout the period of the second test meal, while in 7 others the free HCl reached zero at some point in the second examination. Ten cases showed a moderate reduction, complete achlorhydria occurring in one; in 5 the reduction was only slight and in 4 no reduction of the free hydrochloric acid was brought about. These results appear somewhat erratic, but the result classified as striking can only occur in a patient with a very high acidity before operation; and when we consider all the cases together, classified as showing striking, moderate and slight reduction in acidity, it is found that, with two exceptions, the curve of the free hydrochloric acid after operation is entirely, or almost entirely, within the normal range. The absence of any reduction in 4 cases may have been due to my having failed to tie a sufficient number of blood-vessels. Two of the patients with no reduction in the free hydrochloric acid reported recently, one two years and two months after operation and one five months after; both were well. I would say that, so far as the immediate results of the operation are concerned, an immediate reduction in the free hydrochloric acid occurs in most cases. The operation is probably never followed by persistent complete achlorhydria, which could hardly be expected to follow such a procedure. Whether a state of complete achlorhydria is necessary to ensure freedom from secondary ulceration and whether it is entirely free from harmful effects on the organism as a whole are still matters which are unsettled. Hunt believes that post-operative achlorhydria is not only unnecessary but is highly undesirable, and in performing gastrectomy for duodenal

ulcer he deliberately restricts his removal to one-half of the stomach. He finds that satisfactory gastric function can then be maintained and has not observed anastomotic or jejunal ulcer after this restricted operation. It is possible that Somervell's operation, by the combination of ligation of vessels and gastro-enterostomy, reduces the acidity sufficiently to bring about a satisfactory result. It is necessary to remember, however, that in the past nearly all the suggested alternatives to gastrectomy have failed, one after the other, and it will be necessary to wait for several years yet before we can form an estimate of the true value of this procedure. I certainly do not wish to make any claim for it in the meantime.

In conclusion, the present position in regard to the treatment of duodenal ulcer might be summarised by saying that :—

(1) The treatment is a medical problem in the great majority of cases.

(2) In the case with cicatricial stenosis and a low acidity gastro-jejunostomy gives good results.

(3) For the case without stenosis, partial gastrectomy seems to be the most successful procedure so far evolved. Its ultimate effect on the patient is not yet certain.

(4) In view of the severity of gastrectomy, the possibility of alternative procedures should still receive consideration.

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A CLINICAL REVIEW OF CANCER OF THE BREAST AND ANTECEDENT CHRONIC CONDITIONS *

By ROY F. YOUNG, *M.C.*, M.B., F.R.F.P.S.

THIS title may be somewhat misleading in that this lecture deals mainly with those cases of cancer of the breast which have been under my own supervision during the last twenty years.

Old age has been aptly defined as the time when one begins to seek comfort rather than adventure. There is, however, also a quality of old age in that it has the advantage of being retrospective. I do not mean living in the past—that is senility; but the opportunity of weighing and summing up past experiences for the benefit of those who follow.

It is from this aspect, at a time when one is retiring from charge of hospital wards, that I present this paper. I am deeply conscious of the fact that it contributes little that is original to the subject and that most of what I say must be common knowledge to many.

While this is a clinical review of cases met with in my own experience I attribute my interest and education in cancer of the breast to three men: my old chief, Sir George Beatson, a man who was ahead of his time in his ideas on cancer and who stressed the importance of investigation in the preceding history of cancer cases; Sir Robert Muir, whose pathology on the subject one accepted without question; and Sampson Handley, on whose work all rational surgical treatment depends.

These lectures, given under the bequest of Mrs Helen Thom, were established "for the advancement of the prevention of chronic disease with special reference to cancer"—an ideal based not only on the sound maxim that prevention is better than cure, but on the acknowledged truth that many conditions may be the precursors of cancer.

If by chronic disease is meant some specific disease, then I know of none which can be looked on as a forerunner of cancer; indeed in my experience one striking fact which emerges is that most of my patients have had excellent previous histories of health—almost one might say that cancer appears in the healthy. I know that tuberculosis has been associated with cancer in the opinion of many, and Leaf wrote: "I think that in quite 39 per cent. of cases, and probably more, the development of cancer of the breast should be regarded as to some extent the outward and visible manifestation of the tubercular tendency." One does occasionally come across cases of cancer of the

* A Thom Bequest Lecture given in the Royal College of Surgeons on 5th June 1945.

breast in patients with old tuberculous lesions, but I have certainly not found a greater association of tuberculosis with cancer of the breast than with any other surgical condition.

Where cancer of the breast is concerned I feel that one is justified in substituting the term chronic conditions for chronic diseases as interpreting the meaning of the bequest. To most of you these chronic conditions are familiar, and it is mainly from the clinical angle that I would like to refer to some of them.

AGE.—Age can hardly be classified as a chronic condition, but there are two points with regard to age which are entirely relevant. One is that cancer of the breast commonly occurs during that period in which the breast is undergoing involution—when the machine is past its best—and I do not see that anything can alter it. The mean age of my patients was fifty-four. The other point is that any predisposing agent or carcinogenic agent, whatever it may be, has been in action for a long time before the cancer becomes apparent. It has been shown by Peacock, in experimental production of cancer in animals, that the latent period between the commencement of carcinogenic influence and resulting cancer formation in animals is a long one, equivalent to about one-fifth of the life-span of the individual. It is therefore into the habits and occupations of ten to twenty years prior to the finding of the cancer that enquiry must be made if one hopes to trace any carcinogenic factors in the history of the patient.

HEREDITY, ENVIRONMENT AND HABITS are all matters worthy of research. I think there is little doubt that an hereditary susceptibility of the tissues is an ætiological factor of considerable importance. It is not an easy matter to establish, and I would deprecate a searching examination of the patient on this point; the enquiry should be made through reliable relations. In my own group of cases a family history of cancer was obtained in about one quarter, and one may reasonably conclude that there were many more if accurate family histories could have been obtained.

ERRORS IN LACTATION.—That cancer of the breast is commoner in married than in unmarried women is undoubtedly true, probably in the ratio of three or four to one; but it must be remembered that, at the cancer age, approximately the same ratio is found in all one's female patients. There would, however, appear to be convincing proof that undue prolongation of suckling and refusal or inability to suckle play an important part in subsequent trouble. Leaf, who lays stress on these facts, adds the pertinent comment that "it is a well-known physiological law that, for secreting cells to maintain a state of health, it is essential that the products of their secretory activity should be removed."

TRAUMA.—The term "chronic irritation," which is a recognised precursor of cancer, may include such a variety of different influences that I prefer to classify trauma by itself as a possible carcinogenic influence and discuss it under two headings.

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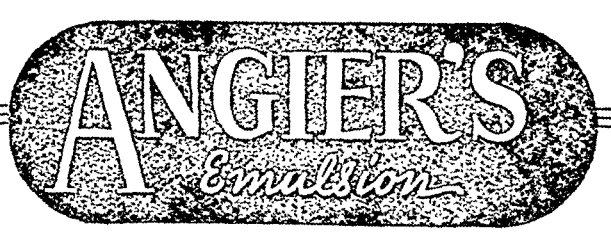

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[1] *B.M.J.* 1915, *ii*, 11.

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A Single Trauma.—It is extremely difficult to assess this with accuracy. Where a gross trauma has been inflicted leading to a hæmatoma of the breast which may, or may not, have required an incision, I have not known of a single case in which cancer of the breast has subsequently developed; nor have I obtained such a history in any of my patients. It is of course the rule rather than the exception to get a history of mild trauma, but my own conviction has been that most patients have sought for a reason after the cancer has developed, much as mothers, whose children have been born with some deformity, seek to find a reason in some association during the pregnancy.

Since reading Sir Robert Muir's Lister Lecture, however, I have been given a fresh outlook on this matter. He has clearly demonstrated how hyperplasia in the breast may, through a series of changes, lead to an intraduct cancer where the cells have the character of malignancy but are held within normal bounds—"a sort of pure culture of malignant cells but still within the test-tubes": eventually the cells break through and infiltrate. When the acini are affected this break-through will occur more readily owing to the slighter resistance offered by their walls. He adds: "From a picture of malignant cells within the mammary ducts one can readily understand how trauma may set up an actual invasion." This could readily explain how a single trauma could hasten, *not cause*, a cancer in the breast.

Repeated (Chronic) Traumatic Irritation.—It is well known that this may lead to cancer formation. The epithelioma of the lip in the clay-pipe smoker, irritation of the tongue by defective teeth are well-known examples.

In the breast there was one type of cancer which used to be fairly common, a scirrhus cancer in the lower, inner quadrant where the whalebone of the stays continually pressed. This type of cancer has now disappeared. There is, however, another interesting possibility, which was pointed out by W. J. Mayo, that cancer of the breast occurs in civilised women, but in those countries where the breasts are exposed and unconfined, it is rarely found. How fashion dictates the environment of the breast can be readily seen in looking back through the volumes of *Punch*—from the time of Du Maurier with the small waist and upper pressure on the breast, then the period when fashion dictated the cylindrical form of the body, with general compression, down to the present time when a natural and rational dress prevails.

PREVIOUS DISEASE IN THE BREAST.—Probably the commonest disease in the breast is abscess. I have investigated this as a possible forerunner of cancer in my cases, and have found, rather surprisingly, that it seems to play little or no part in the subsequent development of cancer.

This has also been my experience with regard to simple tumours of the adenomatous type. I have not come across a single case in which a simple tumour has been removed which has subsequently developed cancer; nor in any of my cancer cases has there been

one in which a simple tumour had previously been removed. This was also the finding in an investigation on this point in the Mayo Clinic.

When one comes to the question of cystic disease as a precursor of cancer in the breast one reaches a subject on which there is a great diversity of opinion. The really practical question with which a surgeon has to deal is how best to treat this condition. Should one advise a local removal or the removal of the whole breast? It is a question which is a recurring problem to all surgeons, and I think it is right that I should state quite definitely what are my own convictions and my own procedure. My view then is that it is *not* necessary to do more than removal of the affected segment, except in such cases in which one finds on examination to have spread widely throughout the breast —in other words, where one has found a cystic condition confined to a segment, removal of that segment is the right line of treatment; in those cases where there is obvious involvement throughout the breast, then the breast should be removed; in young people with a general chronic mastitis there should be no operation at all, though such patients must be kept under periodic survey. As some reason for my opinion—and I am only speaking from my own experience—I can state that I have never come across a patient, on whom I have done a partial resection, who has returned with a subsequent cancer. I must, however, admit that the follow-up of these patients has been imperfect. Further, I have never had to operate on a case of cancer of the breast where a previous local operation for cystic mastitis had been performed.

I must qualify these remarks. There was one patient, aged 44, who had a widespread cystic mastitis of the breast, where I removed the breast. The pathological report was "diffuse hyperplastic changes with new formations of lobules and numerous acinar cysts. No malignancy." Four years later I saw her with a small movable swelling near the axilla. This was removed, and the report was "intra-duct and scirrhus carcinoma. The surviving breast tissue shows marked epithelial hyperplasia and the appearances suggest that malignant change has supervened on a condition of chronic mastitis." The obvious explanation is that I had failed to remove the axillary tail of the breast at operation. It also shows that cancer *can* develop in a widespread cystic mastitis.

More definite statistics on this point have been given by the follow-up in the Mayo Clinic on cases of chronic mastitis which had undergone local operations. Therefore it was found that 3·3 per cent. subsequently developed cancer.

HORMONES.—I am not qualified to speak on this subject with any authority as my personal experience is so limited. I would go further and say that no one is as yet qualified to give an authoritative opinion. This line of treatment is still in the experimental stage and must await full details based on sufficient numbers and on time. Nothing should

be condemned more than a statement of a cure for cancer which has not been adequately confirmed.

It is interesting, however, to remind this Edinburgh audience of the work done by Sir George Beatson at the beginning of this century when he was removing the ovaries in advanced cases of cancer of the breast, his view being that " ovarian secretion formed a stimulus for cell proliferation." Forty years ago he read a paper before the Edinburgh Medico-Chirurgical Society on the influence of ovarian on cancer of the breast. More recently Herrell, in the Mayo Clinic, showed that women who have had complete oophorectomy done are less liable to develop cancer of the breast. Research on œstrin and ovarian influences are still under investigation.

I would now like to review some aspects of cancer of the breast which are more definitely in the province of the surgeon.

Diagnosis

I do not think that there has been great advance in recent years, not because of any lack of interest or intelligent observation but simply because the points in diagnosis have been so well established by our forbears. Perhaps our text-books err in that they still stress the signs of advanced cancer too markedly. The only sign of early cancer of the breast is a lump in the breast, if one may leave out the question of discharge from the nipple. There is no established test for cancer comparable to the Wassermann test for syphilis, and, as things are at present, the person most capable of giving an opinion both as to diagnosis and prognosis is the senior surgeon of experience.

There are two methods, however, which have come into use during the past twenty years which have proved of value in diagnosis. One is transillumination of the breast, which has been used for a long time in diagnosis of hydrocele and the sinuses. With the use of the Cameron lamp, in a dark room, cystic conditions of the breast are readily shown up. Many of us must remember cases in which a palpable, deep-seated cyst of the breast has been mistaken for a carcinoma and a radical operation done where a local operation would have been adequate. It can also be of help in the diagnosis of a hæmatoma of the breast, as Cutler points out. In this condition the opacity is intense and, if it is subsequently examined at frequent intervals, the opacity diminishes in intensity and finally disappears. The other is the immediate histological diagnosis at the time of operation. There are occasions when a definite opinion as to the nature of the tumour is not possible where this method, made within a few minutes, enables one to carry out the appropriate operation which the condition demands. It has the additional benefit of saving the patient from a possible second operation.

Prognosis

It is not necessary to dwell on the various factors on which prognosis is based; they are all well known. Of these the most important obviously is as to how far the cancer has spread. Without going into details three main stages are recognised: Stage 1, where the cancer is still confined within the breast; Stage 2, where spread has taken place via the lymph stream to the axillary glands; and Stage 3, where a wider spread by lymphatic permeation and the blood stream has occurred. Some years ago I collated the results of operation of patients in my wards, each case having been followed for a subsequent period of five years if alive. In Stage 1 there were 87 per cent. of patients who had satisfactorily passed the five-year standard; in Stage 2, only 33 per cent.; while in Stage 3 there were none.

There is, however, one point to which I would like to draw attention as a possible error in classification, namely, the condition of the axillary glands. There is only one method of knowing whether they are involved in secondary spread or not, and that is by microscopic examination; enlarged glands are not necessarily the seat of secondary deposit and many cases in which the glands are not palpable reveal secondary growth on examination of the glands after operation. For example, in the series of cases mentioned above, in which the glands were systematically examined, it was found in Stage 1 that 29 per cent. had palpable axillary glands which proved to be cancer-free on examination; while in Stage 2 there were 25 per cent. in which palpable glands had not been detected before operation, but which, on subsequent examination, showed involvement of the glands by cancer.

Pre-operative Treatment

There is no necessity to dwell on the routine treatment except to state that cancer patients should not be subjected to preliminary starvation and purgation; that is the treatment of a concentration camp and is not suitable for women who have to undergo operation for cancer of the breast.

There is, however, one form of pre-operative treatment which is of the greatest importance, and is often, I fear, neglected. I refer to psychological pre-operative treatment, which requires no expert knowledge and is within the power of all of us. We are all aware, or should be aware, that a woman with a tumour of the breast and who is awaiting operation is bearing a heavy mental weight. She must receive the greatest care and consideration and the surgeon must gain her confidence. Privacy on examination and the avoidance of discussion of the condition before the patient must be punctiliously carried out. If the patient is treated with cheerful reassurance and consideration and has confidence in her surgeon, she will respond with pluck and confidence.

TREATMENT

Recently I heard a comment that there had been little advance in the treatment of cancer of the breast since Halsted's operation. This is of course quite inaccurate. A really big advance in treatment dates from the work of Sampson Handley. His book is a wonderful and painstaking work of constructive pathology, and one must read it in order to understand the centrifugal spread of cancer by permeation if one wants to understand the process. On this depends the entire planning of the operation, or the area to be dealt with if radio-therapy is employed.

SURGICAL OPERATION.—This is carried out as advocated by Handley, but for some years now I have modified it in one respect in that I do not remove the pectoralis minor except in those cases in which the growth is situated in the upper and inner quadrant. With suitable retraction it is quite easy to strip the fascia from the muscle and clear the areas above and below this muscle. There is no doubt that it helps to stabilise the shoulder and give more strength to movements. Then also I have in a good number of cases, when the patients were elderly and debilitated, left the pectoralis major also, being particular however to remove all the fascial planes emphasised by Handley and the axillary glands. It is an uneasy thing to depart from a standard line of treatment, but I have been impressed by the results, which appear to be as good as when the pectoralis major was removed. I feel sure it is worth further investigation.

RADIUM.—In one respect the employment of radium is a definite advance on operative surgery in that it is not destructive. In certain regions, the mouth and cervix uteri for instance, it has largely replaced operation. The point is, however, whether in cancer of the breast it gives results which are as good as operation. In my experience this has definitely not been so. I think it should be reserved for those patients who, for various reasons, are unlikely to be good subjects for surgical operative risk.

RADIO-THERAPY.—I am not prepared to offer an opinion with regard to this form of treatment *per se*. The only patients of mine who have been so treated have been those who were looked upon as inoperable, when one hoped there might be some palliative benefit, or because of the psychological effect of something being done. It would be unfair to assess results on these cases. One does hope that in the future the technique of administration may so develop that it may become the treatment of choice. One drawback is the length of time the treatment takes and the discomfort it causes, so much so that at times it is difficult to persuade the patient to last the course.

OPERATION FOLLOWED BY RADIO-THERAPY.—This has been my line of treatment for the past nine years, ever since I found how unsatisfactory operation treatment results were in those cases in Stage 2. I regret that at present I cannot submit actual figures

showing results because the exigencies of the war-time period have not permitted time for a careful weighing-up of results. I can state, however, quite definitely that there has been a definite and encouraging improvement.

McWhirter, in his Honyman Gillespie lecture, has shown very clearly the great improvement which has resulted from post-operative radio-therapy. He gives a very striking and interesting table of results comparing radical surgical removal of the breast followed by radio-therapy and simple mastectomy followed by radio-therapy. It is true that his results are based only on a single year's standard—and I deprecate the publication of statistics on any other standard than the five-year one, which is everywhere accepted as a reasonable comparative basis—but one cannot but be impressed by the fact that radio-therapy improves the prospect of a cure very materially; also that "simple mastectomy" followed by radio-therapy would seem to promise results as good as those of radical operation followed by radio-therapy.

HORMONE TREATMENT.—I have already pointed out that this line of treatment is still in the process of investigation, and that we must be content to await considered scientific examination and opinion. It is most unfair, and indeed cruel, that a "cure" for cancer should be published before it has been passed by critical and formed scientific opinion. The following case, which seems to give some confirmation to Beatson's view on the effect of ovarian secretion on cancer of the breast, is one of interest.

The patient, aged 39, had the right breast removed by radical operation in 1939 for advanced scirrhus cancer with extensive involvement of the axillary glands; this was followed by radio-therapy. In January 1943 the other breast had to be removed for the same thing. In June 1943 she returned very ill with tense ascites, when many pints of fluid were aspirated, the fluid showing breast cancer cells. She was then given radio-therapy treatment to the abdomen and subsequently the fluid had to be aspirated on several occasions, after which it ceased to reaccumulate. When seen in June 1945 she seemed to be perfectly healthy in every way. Menstruation had ceased since the treatment of abdomen by radio-therapy.

SUMMARY

In a twenty years' clinical survey of cancer of the breast the following considerations are ones which seem to merit further study.

1. Cancer arises in the breast most commonly during the degenerative period of involution. Is there any probability of finding a line of treatment obviating this as a carcinogenic influence?

2. Carcinogenic influences take a much longer time to develop cancer than has been realised. Enquiry into the previous history of a cancer patient, a matter of real importance, must then go back for a considerable period of the patient's life.

3. Chronic trauma to the breast, such as compression or localised pressure, must be avoided.

4. Where chronic cystic disease of the breast is present operation is advisable; where a large cyst is present, or the condition is limited to a segment of the breast, local removal is sufficient. Where it is widespread throughout the breast then removal of the breast only is probably the wise treatment.

5. At the present time the best treatment of cancer of the breast is radical removal followed by radio-therapy, but it would seem to be rational that a modified form of operation, in which the pectoral muscles are left and radio-therapy given later, should be given a full trial; but it should embody all the principles of Sampson Handley's teaching and the fascial planes and the axillary glands removed.

6. Hormone treatment, which seems to promise much, must not be allowed to be announced as a " cure " until it has undergone the acid test by credited clinicians.

7. In advanced cases radio-therapy employed to destroy the ovarian secretion is worthy of trial.

POST-OPERATIVE PULMONARY COMPLICATIONS *

By C. KELMAN ROBERTSON, M.D., D.P.H., F.R.C.P.

LOOKING back on this subject of post-operative pulmonary complications over a period of years we find that in the late nineteenth and early twentieth centuries the lot of the anæsthetist was not an easy one because of the opprobrium cast upon him as a result of the very great frequency of such developments following upon all kinds of operations. A certain amount of frank criticism was probably justifiable since we know, in retrospect, that the art of anæsthesia was at that time in its very infancy, and that many cases must have been unwittingly subjected to the inhalation of soluble lipoid narcotics without considerations which we now, in the light of present knowledge, would deem absolutely essential.

From the latter half of the nineteenth century until the first decade of this present one the most formidable post-operative pulmonary complications were regarded as those of a purely irritative variety, irritative because they arose as a result of inflammation of part or whole of the respiratory tract either by direct contact with a volatile anæsthetic or by organismal infection carried thereto from the higher respiratory regions.

To-day, with the marvellous refinements of anæsthesiology, few, if any, really bad cases of this irritative type are seen. This is not to say, however, that we do not encounter patients who have an attack of acute tracheo-bronchitis, bronchitis or even broncho-pneumonia, after the anæsthetic. We do, but if such a condition does appear, we feel that it has probably been partially existent before operation, and has flared up by some chilling process—a fact so well stressed by Sir Robert Hutchison [1] many years ago.

There is, at the present time, little or no chance of witnessing vivid scenes such as were described in the earlier literature,[2] where the over-deeply anæsthetised patient lay on the operating table, gagged, mouth and nostrils spuming with blood-tinged frothy secretion which carried down churned-up septic matter to the deepest interstices of his lungs. Even if such dramatic scenes were to arise it is always possible that the chances of gross pulmonary infection would be very much less because of the healthier state of the mouths and throats of our present-day generation.

Bronchitis as a result of irritation plus organismal infection, and most certainly broncho-pneumonia following upon the regurgitation of vomited matter, played for some time a leading rôle in the post-operative worries of the surgeon of thirty or forty years ago.

* A Honyman Gillespie Lecture, delivered in the Royal Infirmary, 21st June 1945.

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It was, however, during this anxious phase in the history of our profession that physicians began to take note of the fact that the whole blame for such post-operative pulmonary complications could not always be laid at the door of the anæsthetist, and this realisation called forth spirited appeals from many quarters, especially one by Pasteur,[3] who frankly stated that as those developments were medical in their nature and manifestations they had no real appeal to the surgeon, and that if physicians were more frequently granted the opportunity of studying the initial stages of such upsets, then and then only would additional light be thrown on their nature and consequently upon their treatment.

From the purely clinical standpoint, therefore, we can regard some time during the first ten years of this century as the dawning of realisation that pulmonary emboli appeared as a sequel to many operations. Not that such a possibility had not been mooted much earlier, because the part played by passive congestion of the lungs as a cause of pulmonary infarction had already been noted.[4]

Probably one of the most outstanding and interesting communications on this subject was an article [5] emanating from the Mayo Clinic in the year 1912, wherein attention was drawn to the fact that of all the major operations carried out in that institution between the years 1889 and 1899 there was not one fatal case of post-operative pulmonary embolism, whereas in the following ten years no less than 47 fatalities had arisen from that cause and that alone—a sudden explosive development of no mean significance within a period of ten years, which obviously warranted the most careful scrutiny and investigation. Of recent date, however, it has unfortunately but nevertheless authoritatively been stated that of every 50 patients operated on 1 will develop some kind of pulmonary complication and, more tragic still, 1 out of every 185 of those who develop such a complication will die.

Curiously enough in this field the realisation that embolic phenomena could be a cause of great anxiety and discomfiture was not the only vicissitude that was being encountered, because gradually developing was the understanding that " active massive collapse of the lung " was taking its share in adding to the extra burdens of the surgeon. It was not, however, until 1920-21 that apneumatosis as an entity was satisfactorily placed in the category of post-operative pulmonary complications.[7] [8]

The chronological order of events, then, on this subject can be viewed as (1) irritative upsets, (2) embolic manifestations, (3) atelectatic phenomena. Unfortunately this does not complete the picture, because to-day we know to our cost that another offender has arisen in the form of that distressing and sometimes tragic calamity known as " acute pulmonary œdema."

It is generally accepted that lower abdominal and gynæcological operations furnish us with the greatest number of post-operative pulmonary complications, and I have, thanks to the courtesy of Dr

W. F. T. Haultain and his staff, been able for some time to observe practically all such maladies that have arisen in his gynæcological wards.

A period of two years, from June 1943 until the beginning of this present month, was selected for scrutiny, and during that time 1819 operations of all gynæcological types have been performed, and it has been found that of this grand total only 20 patients have developed pulmonary upsets which have occasioned any serious reaction demanding definite medical therapy.

There have, of course, in addition, been a number of minor respiratory tract infections, but they have generally been of such a simple character that it would be specious to consider classifying them as true post-operative pulmonary complications.

Of this group of 20, 11 have been clinically due to pulmonary embolism; 2 have died, but it must be pointed out that with those 2 fatalities the age factor merits some consideration because both were well past the meridian of life, one being 59 and the other 70, a finding which is in accordance with general opinion, as massive embolism is known to be a disease of later life.

Forty-seven years was the average age for this development, actually a little older than that stated in one of the most recent analytical reviews [9] on this subject, where 44 seemed to be the most susceptible mean in years. Acute attacks of bronchitis accounted for 7 of our patients, and they were all of a fairly well marked type because it was noted that each had a tendency to obesity. I have no note of tobacco-smoking as an aggravating factor in these cases, but I understand that the incidence of bronchitis after operation is six times greater in smokers than non-smokers.[10] Again, in this small group there was one fatality. This, however, was a patient of 80 years of age who had very marked evidence of cardiac degeneration as shown clinically by auricular fibrillation.

One case developed an empyema of a pneumococcal type, and it is not very difficult to assess the part that could have been played by an earlier unrecognised *infarction* which may quite well have been overlooked. Acute pulmonary œdema was responsible for one of our most exacting and worrying cases.

Now, of those cases of pulmonary embolism it was noted that the time of onset was very much later than has been previously recorded,[11] because this episode did not appear in our cases until between the tenth and eleventh day.

The clinical features of all cases were typical, there being a premonitory increase in pulse, temperature and respiration soon followed by pleural pain which directed attention to the affected part. I feel, however, that although this is the normal sequence of events, we do not always recognise the appearance of an early slight unproductive cough, which may arise before there is any complaint of pleural pain. I cannot account for this bronchial reflex, which it

must be, beyond supporting the view [12] that there may be an associated bronchospasm with pulmonary embolism, and that this bronchoconstriction is an early form of vagus reflex.

That the sputum is blood-stained following upon infarction is well recognised, but it must be remembered that this is by no means always so, as actually staining was only evident in six of the cases.

The possibility of pneumonia arising in the area of pulmonary apoplexy, either as a result of infection being carried thereto by the air passages, or pre-existing in the traumatised site, is one that is fast disappearing because of the early use of sulphonamides. In this series, however, one such development must be admitted, namely, the case of pneumococcal empyema.

Unfortunately, in these times, it was not possible to have regular, serial, routine X-ray examinations carried out, which would have assessed the true size of the infarctions dealt with, and would also have verified whether or not any of these cases had small pleural effusions, not that such a development is expected with pulmonary embolism because it is known that effusion is the exception rather than the rule in such cases.[13]

As far as massive death-dealing emboli are concerned, it is of some comfort to consider the two such unfortunate incidents as unavoidable calamities of surgery due to age and failing circulation, in spite of the fact that the number of cases of pulmonary embolism with death following upon operation is really increasing.

Thanks to Dr Robertson Ogilvie, it has been possible to verify this fact by working out the percentage increase of cases of pulmonary embolism coming to the Pathology Department between the years 1939 and 1943, and it has been ascertained that this increase is 1·1 per cent. That this is absolute and not relative is proved because there were 141 fewer autopsies performed during 1943 than in 1939.

The outline of treatment has, in all cases, been purely empirical. We have allayed pain, counteracted shock, and always considered it wise to improve the general circulation as far as possible because it has been claimed that cardiovascular insufficiency is present in anything up to 95 per cent. of patients with pulmonary emboli.[14] No particular dietetic régime has been instituted, excepting liberal supplies of fluid to overcome dehydration, although it is probably wise to recommend a low protein, low fat dietary as such is the type known to be least conducive to thrombotic change.[15]

In view of recent reports [16] there seems little doubt that synthetic anticoagulants, like dicoumarin or dicoumarin plus heparin must in future play an important part in the prophylaxis of such ailments. The question at the present time is to decide whether or not *all* people prior to operation are to be safeguarded by the use of these drugs, because after all it is always possible that any case may develop a pulmonary infarction even while lying on the operating table.

" Thrombophile " suspects could, of course, probably be recognised

by doing daily blood platelet counts and by watching for a decrease in or even constantly checking the erythrocyte sedimentation rate, both of which procedures may give some indication of impending clotting, but this does not get over the difficulty of a thrombus arising with resultant embolus at the time of operation.

In search of a common ætiological factor such points as (1) age, (2) the general condition of the patient, (3) the type of operation, (4) the amount of blood loss, (5) an enfeebled circulation, (6) the evil sequelæ of rest—in so far as they affect lack of proper lung movement and blood stasis, (7) interference with the body's heat-producing mechanism as a result of the type of anæsthetic used, etc., have been considered, and the only factor common to all cases is *age*. If this is so, then surely we must conclude that lack of cardiovascular tone plays an all-important part in the production of such phenomena, and if we accept that, then one of our prime objects of prophylaxis and treatment must always be to ensure a satisfactory maintenance of blood pressure level. This, of course, can be attained best by (*a*) early active and passive movements on the part of the patient as soon as is consistent with comfort after an operation; (*b*) enforced hyperventilation of the lungs by deep-breathing exercises; (*c*) the reduction of the use of narcotics to a minimum. (This I would stress as a most important point. I have frequently discussed this subject with Dr John Gillies, and he also holds strong views on post-operative narcotic abstention unless it is absolutely imperative); (*d*) the judicious use of such drugs as atropine, aminophylline, methedrine, thyroid and digitalis.

There were no actual cases of pulmonary collapse to record in the present series under review, but four such patients were examined during the last two years, both in private and hospital practice. In each case a basal narcotic had been administered prior to the induction of complete anæsthesia, and with this form of present-day technique the likelihood of apneumatosis developing is always very much greater,[17] no doubt due to such factors as prolonged respiratory centre embarrassment, reduced ciliary action of the bronchi, diminished vital capacity of the lungs, etc.

That true collapse appears only when there is absolute bronchial occlusion is an accepted fact, the more viscid the sputum the greater the tendency to collapse, but it would seem that this is not the only factor essential for its production because there must always be an unimpaired circulation of blood in the lungs as well,[18] and no doubt that is why we find this condition arising more frequently in young healthy adults than in older people.

The clinical features of collapse are outstanding and, above all, dramatic in their suddenness, so much so that there is usually, with care, little difficulty in realising that the change is one that has been brought about by a mechanical event rather than by a gradual pathological process.

Other conditions that may possibly simulate apneumatosis are

(1) pulmonary embolism, (2) lobar pneumonia, (3) spontaneous pneumothorax. Probably the most important guide in arriving at a diagnosis —in addition, of course, to the critical examination of the chest where we find a local dull note, mediastinal shift, absent or weak tubular breath sounds—is the fact of observing that the type of respiration is jerky, twitching or spasmodic, due to tonic irritative contractions of the diaphragm. In addition to this we see that the patient has little or no fevered colour of the face; if anything, he is cyanosed and his skin has not the hot, parched dry look that occurs with a temperature. There is invariably in these cases an acute compensatory emphysema of the contralateral healthy lung, and it is because of this that acute spontaneous pneumothorax enters into the differential diagnostic field.

The obvious line of treatment here is to displace the plug of viscid mucus obstructing the bronchus, and this can be accelerated most easily—assuming we have not to have it removed mechanically by means of the bronchoscope—by (1) simple postural coughing, (2) making the patient take good deep breaths. To encourage this latter procedure we would recommend the inhalation of CO_2 because of its action on the respiratory centre, but before doing so it is essential to see that as much mucus as possible is removed from the bronchial tree, otherwise we shall only aggravate the condition by causing hyperventilation and the sucking of secretion deeper down into the tubes. Actually it has been found that the constant therapeutic use of CO_2 increases the incidence of collapse by about 1·2 per cent.[19]

Drugs are of little or no avail as far as collapse itself is concerned, but we must always remember that patients who are harbouring pneumococci in their bronchi prior to operation are the very ones who are most prone to pulmonary collapse [20] and, therefore, suitable sulphonamides should always be given.

Collapse is probably one of the least serious of all the post-operative pulmonary complications, but it must be borne in mind when dealing with this condition that it should be regarded as a manifestation of exhaustion plus a very serious lung insult, both of which warrant very careful and judicious handling.

And now, finally, there is the condition of congestion which in many post-operative cases can soon be followed by acute pulmonary œdema. This state of affairs is, of course, due to leakage of a serous transudate seeping through not only the active capillary bed of the lungs but through the whole of the reserve capillary structure as well, and when it does arise it means that every pulmonary capillary is exuding fluid into the interstitial tissue.

The factors which can be considered as playing a part in bringing this change about after an operation are (1) hypoventilation with resultant lung rigidity; (2) impaired circulation and consequent lack of proper oxygenation or, in reality, a developing state of anoxia; (3) a possible temporary reduction in the output of the left ventricle, which must, of course, materially upset the fine degree of balance

existing between the two main chambers of the heart and which is so essential for normal pulmonary circulation.

The symptoms of pulmonary œdema are, of course, dependent upon the degree of congestion present. In an acute case we find a feeling of apprehension and faintness on the part of the patient, to be followed by a consciousness of oppression in the chest and ultimately an obvious fight for breath by a cyanosed shocked individual expectorating profusely blood-stained frothy sputum.

During the time that this series of cases has been under review I have observed two such really bad cases, both of which have been most alarming in their manifestations, and although I do not include them in this group they were post-operative in that both followed upon Cæsarean section. It may be, as this operation was carried out on account of eclampsia, that a toxic element, emanating either from the kidneys or the pregnancies, was the cause of these pulmonary catastrophes.

The well recognised treatment for such sufferers is (1) oxygen, (2) venesection, (3) morphia, (4) atropine. That oxygen in high concentration should be given to every case of pulmonary œdema is well understood because it has been said that one of the basic causes of this condition is lack of oxygen, and therefore this deficiency must be made good at the earliest possible moment.

A propos of the necessity for immediate oxygenation, it is interesting to recall no less an authority than Drinker's veritable diatribe on this subject, wherein he says that, from what he has seen experimentally, if we decide to give a man oxygen (O_2), it is his belief that we are usually about twelve hours late in our administration because the correct time to start using O_2 is before we think it necessary.[21] A pretty cogent admonition to any who would vacillate about oxygen therapy.

As for venesection, the real value of this old-fashioned but nevertheless useful method of treatment is most apparent in cases where both arterial and venous pressures are raised—a state of affairs, of course, which is not really present in acute pulmonary œdema—nevertheless it cannot be denied that it may help, and as we are in such cases dealing with a real pulmonary emergency, we are surely justified in attempting any procedure that is sometimes beneficial. I may say my own impression is that it is not of very much good in acute pulmonary œdema, as I have seen one or two people bled where the result did not come up to expectations.

The use of morphia is naturally one that is disputed because pharmacologically we know that the alkaloid depresses the respiratory and cough centres, and that its effect in the beginning is one of stimulation of the medullary centre for bronchial secretion. To a certain extent, however, this sedation of the respiratory centre is one of the very things we are aiming at, because it has been proved experimentally that severe respiratory movements have a tendency to produce pul-

monary exudates and therefore we must, as far as is possible, appease this irritated cerebral focus and accordingly give small doses of morphia so as to reduce pulmonary exudation as far as is possible.

The use of atropine in adequate and repeated doses is one that can be emphasised safely, because I am sure it is of no use giving one or two haphazard doses of this drug and expecting a lasting effect. Actually with both cases of acute pulmonary œdema that I have mentioned, we have had to atropinise these patients to the full over a period lasting three to four days and using doses of $\frac{1}{50}$, $\frac{1}{75}$ and $\frac{1}{100}$ gr. every two to three hours. Both patients naturally showed some degree of atropine poisoning—tachycardia, dryness of the mouth, difficulty in swallowing and rash. It is possible, however, that with the doses we were using over this length of time that urinary excretion of the drug was hastened because mercurial diuretics were being used as well, and therefore toxicity was to some extent partially counterbalanced. There is, I am sure, no doubt whatsoever that the inhibitory action of atropine on the receptors going to the mucous glands of the bronchi is the ideal form of treatment for acute pulmonary œdema because its administration is in a very short time followed by dramatic relief, but we must be prepared to continue with its use if necessary over fairly prolonged periods, and even at the expense of obvious toxic side effects.

In conclusion, I have made no attempt during this lecture to correlate the type of anæsthetic used with the incidence of pulmonary upsets, because this particular branch of study is more applicable to the considerations of the anæsthetist than the physician.

I should note, however, that the anæsthetic of choice in practically all Dr Haultain's cases was nitrous oxide, oxygen and ether, probably one of the safest general anæsthetics in use to-day. This, however, was not given to the three patients who died, because two had spinal anæsthetics and one had cyclopropane.

I should again like to express my thanks not only to Dr Haultain for granting me the privilege of seeing many interesting chest cases, but also to Dr John Sturrock for his unfailing co-operation. To Sister Mackay I would also express gratitude for her many kindnesses to a visiting physician.

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THE USE OF PENICILLIN IN ACUTE INFECTIONS OF THE HAND

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IN January 1944 an investigation was commenced to determine the efficiency of penicillin in acute infections of the hand. In view of the large number of cases encountered, there were omitted, with few exceptions, minor infections such as paronychia, early pulp and subepithelial infections and those seldom requiring surgical intervention such as lymphangitis, cellulitis and hair follicle infections. During the last eight months attention was directed to the most serious types of infection.

The total number of cases now reported is 300, including an adequate series of controls. The criterion of healing was the complete closure of a wound without any surface moistness or granulation tissue. The time of healing was reckoned from the day of the original operation, and, in the event of more than a single incision, the slowest to heal was chosen.

The only previous investigation of a similar nature was that of Florey and Williams (1944), to which reference will be made in Tables I and II and in the Discussion.

METHODS OF TREATMENT

(1) *Penicillin Crude Filtrate.*—Penicillin crude filtrate, of a concentration of 80 units per c.c., was used in 60 cases. At the time of operation, and daily thereafter for a week, it was introduced into the wounds either in lightly packed dressings or through fine rubber tubes, also acting as drains. The effects were uniformly undesirable as the wounds and adjacent healthy skin became sodden and tender and as a heavy growth of coliform organisms appeared. There was a marked tendency for granulations to be absent and for epithelium to grow down into the depths of a wound, producing indolence and finally a depressed ugly scar. The results were not as good as in the control series and are not reproduced here. Without hesitation, penicillin crude filtrate is to be condemned in the treatment of hand infections requiring incision, a warning which seems desirable in view of successes in isolated cases reported by Alston (1944) and Hobson and Galloway (1944).

(2) *Penicillin Lanette Wax Cream.*—This was of a concentration of 500-1000 units per gram of cream and was used in 109 cases, being introduced into the operation wounds daily for a week, when

necessary along a blunt wide bored needle. With few exceptions it gave no better results than control methods.

(3) *Penicillin Powder.*—Most incisions in the hand were unsuitable for the introduction of a powder, and, although applicable during anæsthesia, there was difficulty in repeating it at subsequent dressings, the cream at times having to be substituted. Penicillin dried crude filtrate was sticky and not easy to handle and caused intense pain for as long as half an hour after application. Penicillin and sulphathiazole powder did not have these disadvantages and the results were similar to those given by penicillin cream.

(4) *Penicillin Continuous Intramuscular Drip.*—This method was utilised only in the severe infections, chiefly tenosynovitis. The Eudrip apparatus No. 3 was used, as recommended by McAdam *et al.* (1944), and as a general rule 100,000 units were administered as a daily dose for five days. The wounds were covered only with dry dressings, no penicillin being applied locally.

(5) *Penicillin in Oil or Wax Intramuscularly.*—Penicillin mixed with beeswax or peanut oil was injected intramuscularly twice daily. The findings were not encouraging in 3 cases.

(6) *Control Methods.*—One hundred control cases were included in the investigation and in their severity were strictly comparable to those treated with penicillin. The chief local dressing employed was a 1 in 1000 aqueous solution of acriflavine, but sulphanilamide powder, sulphanilamide cream, magnesium sulphate and glycerine, and vaseline were also used. Frequently applied hot boric fomentations and other moist dressings were avoided.

(7) *Management in General.*—In order to avoid individual variations in treatment all incisions were carried out personally, and so also all dressings were supervised. Standard types of incisions were employed and, except for the actual preparation used, the same treatment was adopted for each group of comparable cases. In the cases treated with penicillin locally no deliberate attempt was made to dispense with incisions by aspirating pus and injecting penicillin into the abscess cavity, and it was noted on occasion that such an injection was not an adequate substitute for an additional incision, if that appeared necessary. Patients were admitted to a ward during the most acute stage of an infection and always for the purpose of intramuscular administration of penicillin.

Sulphanilamide, sulphapyridine and sulphathiazole, given orally, were of definite value in early cases of lymphangitis and cellulitis, but were disappointing in other infections, especially after pus had formed. In fact, their indiscriminate use prior to hospital attention was the cause of much unnecessary delay in surgical treatment, and it should be recognised that too much faith is liable to be placed in them.

The soaking of the hand in hot baths and exposure to dry heat were avoided as being undesirable. The circulation of the infected area was often precarious and sloughing imminent, so that heat in any

form seemed no more justifiable than in cases of vascular insufficiency. Splints were applied in all cases of suppurative arthritis, and in other infections when there was a tendency for the wrist and fingers to be held in bad functional positions. Early active movements of the unaffected parts were enforced and were the best insurance against unnecessary joint stiffness. Except in arthritis, movements of the affected finger were gently encouraged after three days. Physiotherapy was of little or no value and excellent results, even in tenosynovitis, were attained without its use. It caused no improvement in parts already stiff as the result of the infection, nor could it reasonably be expected to be successful then.

Clinical Types of Infection

(1) *Pulp Infection.*—The cases studied were those of moderate severity, those with sloughing of the soft tissues and those with previous ill-judged attempts at incision. The early stages of the infection were omitted, as rapid healing and full functional recovery should be attainable by adequate surgical methods.

TABLE I

	Number of Cases.	Time of Healing (Days).	Time of Healing (Days). (Florey and Williams.)
(1) Pulp infection.			
Penicillin cream	18	23	21
Control	19	18	29
Penicillin intramuscular drip	1*	16	...
(2) Pulp infection with necrosis of terminal phalanx.			
Penicillin cream or powder	8	36	...
Control	8	37	...
Penicillin intramuscular drip	2*	47	...
(3) Subcutaneous infection.			
Penicillin cream or powder	22	17	...
Control	22	15	...
(4) Web infection.			
Penicillin cream	12	13	18
Control	12	16	34
(5) Palmar infections.			
Penicillin cream	14	26	...
Control	13	23	...

* Cases classified under tenosynovitis, which complication followed faulty incision of pulp infection.

(2) *Pulp Infection with Necrosis of Terminal Phalanx.*—Included were all cases of pulp infection in which necrosis of bone occurred, whether present at the time of the first examination or not. Sequestrectomy always proved necessary. If the soft tissues were extensively destroyed an unsightly, disabling claw deformity was the outcome. If not, the functional result was surprisingly good.

(3) *Subcutaneous Infection.*—This was a mixed group of varying severity and usually arose from infected wounds or from the localisation of a cellulitis.

(4) *Web Infection.*—In some cases the infection was well localised, but in others pus tracked widely across the distal part of the palm and also into the subcutaneous tissues on the palmar or dorsal surface of a digit. Recovery was generally uninterrupted and no loss of function resulted.

(5) *Palmar Infection.*—Here were included all infections of the palm deep to the deep fascia, with the exception of those secondary to tenosynovitis or severe lymphangitis. It was not possible to classify them as specific palmar space infections, as in no case was pus localised within these boundaries. Severe systemic reactions were rare and the functional results were all good. The time of healing varied from nine days in an early case to fifty days in a neglected case with extensive sloughing.

(6) *Acute Tenosynovitis.*—A group of 39 cases, this proved the most instructive and gratifying in the whole investigation and received particular attention. The only cases excluded were very late infections with sloughing of tendons or suppurative arthritis already established.

In view of the most encouraging results with the penicillin intramuscular drip, it was decided to pursue this method thoroughly, and a complete series of controls was not continued after the early stages of the investigation. A notable feature was the clean state of the wounds, permitting infrequent dressing after operation at intervals of not less than three days. Rapid healing was associated with admirable recovery of function. Of the greatest importance was the manner in which serious infections of the radial or ulnar bursa or of both were overcome without any subsequent disability. The failures also were instructive and demonstrated the ineffectiveness of penicillin in the more advanced stages of the infection.

Scrutiny of the figures might suggest that penicillin in the form of cream or powder was as satisfactory. In spite of careful daily dressings it was not possible to ensure that it actually remained in the depths of the wounds, and its relative lack of success in the other infections rather weighed against its recommendation.

In every case an operation was performed without delay. The original wound or track was explored. In the case of the 2nd, 3rd and 4th fingers the routine method was to expose and drain the tendon sheath by three separate incisions over the 1st and 2nd phalanges on the lateral or medial side, and in the palm over the proximal end of the sheath; the skin creases and the sheath at these levels were left intact. In 2 early cases the incision in the palm was omitted, whereas in 3 cases with much subcutaneous pus counter incisions were made over the 1st and 2nd phalanges. In 3 cases the incisions in the palm and over the 1st phalanx were joined together, once in order to obtain exposure to remove a piece of needle from the

sheath and twice on account of sloughing at the original site of infection over the proximal crease. In the thumb and 5th finger, similar routine incisions were made in the digit and in the palm; in 3 cases Parona's space was drained by medial and lateral incisions, and in 3 others with early infections they were omitted.

In no case was there difficulty in maintaining full movement of the rest of the hand.

TABLE II

Acute Tenosynovitis

	Number of Cases.										Days.	Days.
		Site.		Complications.				Movement of Finger.				
	Total.	2nd, 3rd, or 4th Finger.	Thumb or 5th Finger.	Sloughing of Skin.	Sloughing of Tendon.	Arthritis.	Amputation for Sepsis.	Complete.	Very Good.	Slight or None.	Average Time of Healing.	Average Time of Healing. (Florey and Williams.)
Control . .	4	4	...	1	1	...	...	...	...	4	32	58
Penicillin crude filtrate	2	2	...	1	2	1	1	...	...	2	60 (1 case only)	...
Penicillin cream or powder	6	6	...	1	...	...	...	2	2	2	30	34
Penicillin in wax or oil	2	2	...	1	1	1	1	...	...	2	19 (1 case only)	...
Penicillin drip .	25*	8	4	...	...	...	...	12	...	...	19	...
		5	2	2	...	...	...	...	7	...	29	...
		6	...	4	2	...	...	...	...	6	42	...

* Arranged according to healing times.

(7) *Suppurative Arthritis.*—Here were considered cases of infection of an interphalangeal or metacarpo-phalangeal joint consequent on a wound involving it. Excluded were those secondary to tenosynovitis or severe spreading infections. The results of treatment were particularly difficult to assess, depending on the source and virulence of the infection and the interval between the injury and the beginning of hospital treatment. Figures of average times of healing are therefore of no value.

One patient with an infected penetrating wound of a joint of twenty-four hours' duration responded at once to rest and sulphathiazole. A second patient, with a similar wound of six days' duration, did not respond to sulphathiazole but obtained a perfect result after the penicillin intramuscular drip; no operation was necessary.

Fourteen other cases of later degrees of infection were treated, 6 with penicillin cream and 8 as controls, all requiring incision. The best figures for times of healing after operation were thirty and thirty-five days for the former and fifty for the latter. In one of the former a slight range of movement was retained, in 9 cases the result was bony ankylosis and in 4 cases amputation was performed.

(8) *Severe Lymphangitis.*—In this section was studied a particularly severe type of lymphangitis, occurring especially in the middle-aged or elderly. A trivial scratch, abrasion or burn was the origin of a hæmolytic streptococcal infection, and a few days later there developed an intense, confluent type of lymphangitis, causing a remarkable degree of swelling of the whole hand and wrist or even higher, and associated perhaps with hæmorrhagic spots or patches in the skin. Localised tenderness at times suggested an infection of a flexor tendon sheath. Of even more importance were the general effects, such as high temperature, rigors, toxæmia and cardiac irregularity. The subsequent course varied as the infection might resolve completely, though slowly, or might progress to form a localised abscess in any site in the hand, wrist or fore-arm.

TABLE III

Severe Lymphangitis

Case.	Treatment.	Localisation of Abscess.	Severity of Infection.	Response to Sulphathiazole.	Response to Penicillin.	Healing Days.	Complete Recovery of Function (days).
1	Penicillin cream	+	+++	Poor	Doubtful	22	60
2	Control	+	++	Poor	...	22	40
3	Penicillin drip	—	++	Poor	Good	...	60
4	Penicillin drip (2 courses)	+	+++	Poor	Good	50*	60
5	Control	—	+	Good	...	...	14
6	Control	—	+	Good	...	...	30
7	Control	+	++	Good	...	12	30

* Relapse after one course of penicillin. Healing and recovery delayed by a burn.

(9) *Spreading or Gangrenous Infection.*—There were encountered 18 cases of this type, either starting benignly and becoming severe, or being severe from the onset. They were characterised by a diffuse, progressive destruction of all the tissues of a digit, with spread of the infection to the palm or dorsum of the hand. Very important constitutional factors were old age, heart disease, diabetes and malnutrition, all of which should be regarded as of evil prognosis in any hand infection. Among the local causes were injuries by fish bones and bites. Apart from any other cause, certain cases seeking attention at a very late stage or after misplaced incisions followed the same course.

Treatment was always unsatisfactory and the infection could not be overcome by adequate surgical measures, local applications or sulphonamides orally. The penicillin intramuscular drip was used in one case without success. Amputation of the digit was the usual fate, carried out because of massive gangrene, intractable sepsis or useless crippling.

(10) *Miscellaneous Infections.*—Penicillin cream proved effective in 14 cases of miscellaneous infections, including furunculosis, septic burns and paronychia. These can usually be treated quite adequately by control methods, but a small proportion are resistant and do benefit from penicillin applications.

Bacteriological Findings

Bacteriological examination of the pus was a routine investigation, swabs being taken from wounds at the time of operation, at the third or fourth day and at lengthening intervals thereafter. Over 90 per cent. of the infections were due to *Staph. aureus* and the rest either to pure *Strep. hæmolyticus* or to mixed Staphylococcus and Streptococcus. In tenosynovitis the proportions of these types were more equal and severe lymphangitis was due to pure Streptococcus.

Using local applications, either control or penicillin cream or powder, there was not any correlation between the type of organism, the organism clearance time, the state of the wound and the final clinical result. Although *Strep. hæmolyticus* might be eliminated in a few days *Staph. aureus* generally persisted until healing. Penicillin crude filtrate was invariably accompanied by a heavy infection of coliform organisms and quite often by a secondary *Strep. hæmolyticus* infection.

Under penicillin intramuscular drip there was a rapid clearance of *Strep. hæmolyticus* by the third day, with a corresponding clinical improvement. *Staph. aureus* persisted for a week or more, a successful clinical result still being attainable. Only one case developed a secondary infection with *Strep. hæmolyticus* and *B. coli*, the clinical result being bad.

Discussion

Uninfluenced by any particular method of local or general treatment, necrosis in the infected parts was the principal cause of retarded healing and disability. It could be traced to errors such as lack of early attention to wounds, too early incision of an area of cellulitis or lymphangitis, prolonged application of hot fomentations and too much reliance on sulphonamides when incisions were called for, and making of incisions without adequate surgical facilities. It was also associated with the factors already mentioned which make for a bad prognosis.

Florey and Williams (1944) applied penicillin locally in the form of cream or powder and claimed conspicuous improvement over control methods, as regards clearance of organisms, time of healing, recovery of function and saving of man-days of working time. In the present series there was no appreciable difference between the methods in the types of infection in Table I, but the control figures of Florey and Williams were definitely worse.

In tenosynovitis Florey and Williams reported excellent results, but noted that full movement at the interphalangeal joints was not regained when pus was present in the tendon sheath. In the present series full movement was regained with both local and intramuscular penicillin, even after the demonstration of frank pus in the sheath. In the former series the thumb was never involved and the 5th finger once only, without detail of the severity or spread of the infection. In the present series there were three particularly severe cases of involvement of the radial bursa, of the ulnar bursa and of both, complete restoration of function being restored by the use of the penicillin drip.

Further trial with penicillin administered intramuscularly is to be recommended in suppurative arthritis and severe lymphangitis, the results in the few cases treated having been encouraging.

SUMMARY

Three hundred cases of acute hand infections were investigated. Penicillin crude filtrate was condemned and penicillin lanette wax cream was no improvement on control methods, except in isolated instances. Penicillin administered by the continuous intramuscular drip was successful in tenosynovitis.

I wish to express my indebtedness to Professor J. R. Learmonth, who initiated and constantly encouraged the investigation. The Penicillin Clinical Trials Committee of the Medical Research Council supplied almost all the penicillin. Dr J. P. Duguid carried out the bacteriological investigations, and, in the closest association with the clinical work, was responsible for important suggestions in the application of penicillin. My colleague, Mr W. A. Coe, co-operated most loyally by transferring to my care a large number of his own cases.

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NOTES

Royal College of Physicians of Edinburgh

At the Annual Meeting held on 6th December 1945, Dr David Murray Lyon was elected President, and Drs W. D. D. Small, C.B.E., L. S. P. Davidson, J. D. S. Cameron, H. L. Wallace, I. G. W. Hill, C.B.E., and D. K. Henderson were elected to form the Council for the ensuing year. Dr W. D. D. Small, C.B.E., was nominated Vice-President.

University of Edinburgh

At a Graduation Ceremonial held on Friday, 14th December 1945, the following degrees were conferred :—

The Degree of Doctor of Medicine—John Harle McIntyre, England, M.B., CH.B., 1934; Oloff Abraham Servaas Marais, South Africa, M.B., CH.B., 1935; James Farquhar Ogilvie Mitchell, Scotland, M.B., CH.B., 1944; Randolph James Elliot Paterson, Scotland, M.B., CH.B., 1911; James Frederic Riley, England, M.B., CH.B. (with Honours), 1935; Anthony Elliot Ritchie,* M.A., B.SC., Scotland, M.B., CH.B., 1940; Ian Murray Scott,† Scotland, M.B., CH.B., 1934; Sheila Patricia Violet Sherlock,* England, M.B., CH.B. (with Honours), 1941; Leslie Melville Thompson, Scotland, M.B., CH.B., 1923; Walter Sneddon Watson, Scotland, M.B., CH.B., 1938.

The Degree of Master of Surgery—Ian Alexander George Lawson Dick, M.D., Scotland, M.B., CH.B. (with Honours), 1928.

The Degrees of Bachelor of Medicine and Bachelor of Surgery—John Campbell Strathie Adams, Scotland; Brian Anstey Cookson, England; Frederick Ewart Cull, England; Andrew Douglas, Scotland; Samuel Clive Dryden, Jamaica; Kenneth Dudley Foggitt, England; May Lois Gilbert, Scotland; Robert Edward Glenn, Scotland; William Henry Graham, Scotland; Keith Antony Reginald Henry, England; William Richard Johnson, Scotland; Ian James Michael Lumsden, Scotland; John Rankine McCallum, Scotland; Donald Laurence Mackay, Scotland; Margaret Mary Macpherson, M.A., Scotland; Eileen Mungall Munn, Scotland; Thomas Mackie Ness, Scotland; Thomas Harling Park, England; David Falconer Robertson, Scotland; David John Rodger, England; Daphne Green Doveton Tillou Smedberg, U.S.A.

Diploma in Medical Radiology—Alexander Adam Ness Bain, M.B., CH.B. (ABERD.); John Raymond Condon, M.B., B.CH. (NAT. UNIV., IRELAND); Ernest Francis Ridley, M.B., CH.B. (ST ANDREWS).

The Polish School of Medicine at Edinburgh—The Degree of Bachelor of Medicine and Bachelor of Surgery:—Jan Jakob Danek, Aleksander Hołyniec, Tadeusz Weckowicz.

* Gold Medal for Thesis.

† Commended for Thesis.

NEW BOOKS

Cookery Book for Diabetics. Compiled by the Diabetic Association. Pp. vii+74. London: H. K. Lewis & Co. Ltd. 1945. Price 4s. net.

The diabetic diet unless carefully supervised is apt to be monotonous, yet diabetics can have an infinite variety of food if proper rules be observed. This booklet has been drawn up to help the diabetic in his choice of food. It consists of some hundreds of recipes for suitable dishes of all kinds. Each recipe gives full instructions for the preparation of the dish and gives the values in carbohydrate, protein, fat and calories. It is a most valuable compilation, which should be of the greatest value to all diabetics.

Pulmonary Tuberculosis. By R. Y. KEERS, M.D., F.R.F.P.S.G., and B. G. RIGDEN, M.R.C.S., L.R.C.P. Pp. xii+273, with 122 plates. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 17s. 6d. net.

The authors, who are physicians at Tor-na-Dee Sanatorium, have had wide experience of the subject and write from first-hand knowledge. The book begins with the historical and scientific background of the subject, then goes on to describe symptomatology, diagnosis, prognosis and treatment in various phases. The chapters on treatment are especially well done, the scope and limitations of each method being clearly set out. The authors, who write in a stimulating and attractive manner, have succeeded in compressing a wonderful mass of information into little space, and the book may be regarded as an up-to-date presentation of our present-day knowledge. The illustrations are mostly taken from skiagrams and are excellently reproduced.

This little book is assured of a warm reception from the medical profession.

Neurology of the Eye, Ear, Nose and Throat. By E. A. SPIEGEL, M.D., and I. SOMMER, M.D. Pp. xi+667, with 118 illustrations. New York: Grune and Stratton. 1944. Price $7.50.

This book is based on a series of post-graduate lectures which were designed to bridge the gap between the specialties concerned and neurology. Anatomy and physiology are fully considered and that portion of the book seems of greater value than the clinical part. The teaching is orthodox, in parts it might be called old-fashioned, and the book would be improved if the authors could find the courage to eliminate out-of-date methods of treatment which have doubtful scientific basis. The style inclines to the ponderous at times, and the free use of italics does not tend to ease of reading as is probably intended. The arrangement of the book and the excellent table of contents renders reference easy, and the very extensive bibliography should prove of great value to the student. The illustrations, though not very numerous, are of a good standard.

François Magendie. By J. M. D. OLMSTED. Pp. xvi+290, with 5 illustrations. New York: Schuman's. 1944. Price $5.

Professor Olmsted's intimate knowledge of nineteenth-century French medicine has followed up his biography of Claude Bernard with one of François Magendie, a generation earlier. The personality of Magendie as one of the founders of experimental physiology and neurology is perhaps less outstanding than the circumstances of academic and professional life in France during and after the Revolution; the undercurrents of personal rancour and professional jealousy governing official recognition and promotion are more evident here than in the latter part of the century. There is a well-documented and impartial account of the

famous controversy between supporters of Magendie and of Sir Charles Bell as to priority of discovery of the function of the spinal nerve roots. The author has succeeded in building up a vivid account of the atmosphere surrounding discoveries which have proved to be at the basis of much of modern medicine.

Die Intravitale Knochenmarksuntersuchung. By Dr STEFAN J. LEITNER. Pp. 386, 189 illustrations and 6 coloured plates. Basel: Benno Schwabe & Co. 1944. Price 36 Francs.

Dr Leitner's book on hæmatology is mainly devoted to the special study of hæmopœisis in a wide variety of diseases as investigated by the modern technique of sternal puncture. The book is a valuable contribution to hæmatology. Both the subject matter and the illustrations are excellent. Dr Leitner is a pupil of Naegeli, and his work maintains the high standard of his teacher. The book is written in German. It can be recommended to all hæmatologists interested in the problems of hæmopœisis.

A Bibliography of Visual Literature, 1939-1944. Compiled by J. F. FULTON, P. M. HOFF and H. T. PERKINS. Pp. x+117. Springfield, U.S.A.: Charles C. Thomas. 1945. Price $3.00.

This book is similar in character to the *Bibliography of Aviation Medicine* issued a short time ago. It contains over 3000 references to books and journals which have appeared during the War years. The articles listed are arranged under many subdivisions so that all recent papers dealing with a special subject are collected together. In addition there are indexes of authors and of subjects. The compilation should be of the greatest service to the specialist and to the medical library.

NEW EDITIONS

Massage and Medical Gymnastics. By MARY V. LACE. Foreword by JAMES MENNELL, M.A., M.C., B.C. Third Edition. Pp. xi+244, with 126 illustrations. London: J. & A. Churchill Ltd. 1945. Price 12s. 6d. net.

This new edition of Miss Lace's well-known manual has been thoroughly revised and brought into line with the latest developments in physiotherapy.

Many of the more obsolete movements have been rightly omitted and new variations of free and recreational exercises have been added.

The book is primarily designed for students in preparation for the examination of the Chartered Society of Physiotherapy. It contains all the basic exercises and manipulations required to give them a solid foundation from which to devise all types of movement, both simple and advanced, for the rehabilitation of the sick and injured.

The illustrations are good and very clear.

Textbook of Medicine. By various Authors. Seventh Edition. Edited by J. J. CONYBEARE, M.C., D.M.(OXON.), F.R.C.P. Pp. 1164, with 21 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 30s. net.

This book, which has become one of the standard works in British Medicine, now appears as a seventh edition, the third since the outbreak of war. The features which have made the previous editions so popular are fully maintained and, if possible, enhanced in this new one. Certain sections have been re-written and some contain additions which add to the completeness of the book. In a work which is so uniformly good it is perhaps invidious to single out any section, but the one on renal disorders

deserves special mention, for so frequently it is the one which both student and graduate find beset with difficulty; for the lucid manner in which this complex subject is presented in the present edition many readers will be very grateful. It is certain that the book will continue to prove a valued possession to practitioners and students, for all the commoner disorders are fully covered, yet not clouded with an excess of detail.

The Elements of Medical Treatment. By Sir ROBERT HUTCHISON, BART., M.D., D.SC., LL.D., F.R.C.P. Fourth Edition. Pp. 213. Bristol: John Wright & Sons Ltd. London: Simpkin Marshall (1941) Ltd.

This book, originally written in order to enable students to approach therapeutics along rational lines and to help them to understand the various measures employed in the wards when first they enter them, has been completely revised in this edition. The introductory chapters remain excellent, but subsequent chapters vary very considerably; some, notably those on the use of endocrine preparations, are very good, but others will doubtless perplex the student, for many of the measures advocated he will not see practised in the wards to-day, and the drugs mentioned in detail in the book have in many instances given way to more potent preparations. A feature of the book which may prove of value to the student is the very complete, and fully explained, prescriptions which it contains; in many instances they are very pretty examples of the art of prescribing, but their therapeutic value in some cases would be viewed with scepticism by many pharmacologists and not a few clinicians.

Acute Injuries of the Head. By G. F. ROWBOTHAM. Second Edition. Pp. xvi+424, with 201 illustrations. Edinburgh: E. & S. Livingstone. 1945. Price 30s. net.

This excellent monograph has been considerably enlarged and brought up to date. There is a new chapter on rehabilitation of the head-injured, which contains much sound advice, and a new section also on the mechanism of birth injuries.

The author has maintained his high standard in presenting his subject. Some would like to see reference made to the wide field for co-operation with the psychiatrist and psychologist in the analysis and management of the various syndromes presented by so many cases of head injury. The time is now ripe for inclusion also of an account of the part which the speech therapist can play in restoring those with disorders of the mechanisms of speech.

The publisher deserves a word of praise for the excellence of the paper, printing and binding.

BOOKS RECEIVED

BAILEY, HAMILTON, F.R.C.S. Demonstrations of Operative Surgery for Nurses. (*E. & S. Livingstone Ltd., Edinburgh*) 21s. net.

BOURNE, ALECK W., M.A., M.B., B.CH. Synopsis of Obstetrics of Gynæcology. Ninth Edition, fully revised . . (*John Wright & Sons Ltd., Bristol*) 21s. net.

BURROWS, HAROLD, C.B.E., PH.D., F.R.C.S. Biological Actions of Sex Hormones . . . . (*Cambridge University Press, London*) 42s. 6d. net.

CURRAN, DESMOND, M.B., F.R.C.P., D.P.M., and ERIC GUTTMANN, M.D., M.R.C.P., Psychological Medicine. Second Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 10s. 6d. net.

JAMIESON, E. B., M.D. Illustrations of Regional Anatomy. Complete Volume. Seven Sections. Sixth Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 75s. net.

UNDERWOOD, E. ASHWORTH, M.A., B.SC., M.D., D.P.H. A Manual of Tuberculosis. Third Edition . (*E. & S. Livingstone Ltd., Edinburgh*) 15s. net.

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